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# NEW EXPERIMENTAL ASPECTS OF THE ANTI-TUMORIGENIC ACTION OF STEROID HORMONES

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It is the purpose of this report to survey the results of our experimental work with the preventive action of steroid compounds against estrogen-induced tumoral growth, and to establish certain implications these findings may have for the understanding of the antitumorigenic activity of steroids in general.

The tumoral growth which has served us in our research on the antitumorigenic actions of steroids has been estrogen-induced atypical growth in the guinea pig and first of all the estrogen-induced abdominal fibroid. It is generally known that this type of growth has been elicited first by Nelson on the surface of the uterus and subsequently though independently by French workers (Moricard and Cauchoix) and by ourselves (Lipschutz and Iglesias). It was our luck to establish that these fibromata and fibromyomata can originate everywhere on the serosa of the abdominal cavity of the guinea pig. Soon afterwards Argentine workers found them also on the thoracic side of the diaphragm (Sammartino and Herrera). We have found thoracic fibroids also far away from the diaphragm.

The abdominal fibrous or fibromyomatous tumor can be elicited with minute quantities of estrogen, natural or synthetic, free or esterified. It is not by quantity but by abnormal timing conditions, *i.e.*, by continuous instead of rhythmic action, that estrogens acquire the faculty to induce these tumors (Lipschutz, Rodriguez, and Vargas). The idea must

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be definitely dropped that for eliciting tumoral growth large quantities of estrogen are necessary.

Doubt may be thrown at the outset on the justification of drawing any conclusions about tumorigenic and antitumorigenic actions of steroids based on work with estrogen-induced epithelial or conjunctive atypical growth. Is this experimental growth comparable to spontaneous neoplastic growth? The abdominal fibroid invades neighboring tissues as malignant tumors do; pancreas, smooth and striated muscles are invaded and even destroyed by this violent growth. But the fibroid regresses after the withdrawal of the estrogen by which it has been elicited; neither is it transplantable. Metastases are not produced. According to the classic and current concept tumoral or neoplastic growth is not only localized, or insular, but also an autonomous, continuous, illimited, irreversible proliferation because of its being supposedly independent of the stimulus by which it has been elicited at its very outset.

It is certain that from the point of view of current terminology estrogen-induced adenomatous growth or the estrogen-induced fibroid is not neoplastic growth. But one must not overestimate the bearing of a terminological concept which is but an approach to, and often very far from, the true image of things. Is prostatic carcinoma still a neoplasm after having been shown by the work of Huggins to be reversible when androgen is withdrawn or when androgen is antagonized by estrogen?

The original stimulus by which an occupational tumor has been induced, or the hydrocarbon by which a subcutaneous sarcoma has been elicited in an experimental animal, is not necessary any more for maintaining further growth of these tumors. But by this fact persistent action of some other causative stimulus called for, or called into existence, by the original stimulus is not beyond possibility. There are also other highly relevant observations with the true neoplasm induced by the hydrocarbon. What later on becomes a transplantable sarcoma seems to be at the beginning simple granulomatous tissue, and what later on becomes an irreversible carcinoma is at its outset a reversible epithelioma as shown by various authorities.

On the other hand induction of irreversible atypical growth through the prolonged action of estrogen is possible though not frequent. We were fortunate to find atypical proliferation of the endometrium in a castrated guinea pig which had been injected with estrogen for eight months and necropsied four months after ceasing to inject the hormone. The genital opening closed as is the rule in castrated females; there was an involution of the mammary glands and the myometrium. There was consequently no manifest source of estrogen in the body—and nevertheless there was atypical epithelial growth of "precancerous" aspect as it is sometimes termed. This case of irreversible growth induced in the guinea pig with the prolonged administration of estrogen was exceptional. But in a strain of mice Allen, Gardner, Strong and others have induced in the same way cancer of the uterine cervix which proved to be transplantable. More abundant are the findings with other tumors. Spindle cell sarcoma has been elicited in mice by Loeb, Lacassagne, Gardner and others at the site of subcutaneous injection of estrogen. But sarcomata may appear also at distance, as on the vaginal wall or urinary bladder. There were in the work of the last mentioned authorities also estrogen-induced lymphosarcomata of the thymus and of the lymphatic glands. Some of these sarcomata were transplantable.

Whereas irreversible neoplastic growth is rarely induced with estrogens it is the rule with hydrocarbons. One may tentatively recur to the explanatory concept of Rous' based on experiments with tar applied to the skin. Neoplastic growth is biphasic. In the first phase atypical proliferation and atypical differentiation of cells is induced but the cells remain normal as to their reactivity. In the second phase the cells acquire the faculty of autonomous growth; but autonomy may be only apparent, a new stimulus, for instance a virus, having been called for or called into existence by the original stimulus. With hydrocarbons the phase of proliferation is rapidly succeeded by the second phase, that is by cancerization. On the contrary, with estrogens the first phase is in general not succeeded, or only exceptionally succeeded, by the second phase. There is much probability that the transi-

tion from the first to the second phase is, with estrogen, time-conditioned. Two time-conditioned changes may be mentioned here. With minute quantities acting during weeks or months endometrial glandular hyperplasia and adenomatous polyps are induced. But when the experiment is prolonged the proliferated glands invade the myometrium and they may reach and even break through the serosa. It is a picture similar to adenocarcinoma in women (Riesco). Indeed, we do not know whether this experimental condition can be identified with adenocarcinoma. The second time-conditioned change was biochemical. A great increase of alkaline phosphatase has been found in the uterine mucosa and submucosa of the guinea pig subject to the action of estrogen for about two months; but then alkaline phosphatase begins to diminish again and even considerably though proliferation continues (Fuenzalida, *et al.*). We are as yet unable to give the just interpretation to this change. It may be simply due to a greater content of water in the thickened uterine submucosa. But the "second phase" in the structural and biochemical, or say behavioral, condition of the proliferating cell under the continuous action of estrogen is a problem to be attacked experimentally. It may be recalled that a definite link between endometrial glandular hyperplasia and adenocarcinoma has been repeatedly claimed by clinicians and pathologists. Has the original estrogenic stimulus nothing to do with the break from benign to the malignant condition? Does this stimulus really cease at the start of the malignant condition? Is the estrogen which is produced in the suprarenal of no implication in adenocarcinoma in women in old age?

We have as yet not been able to establish any fundamental time-conditioned change with estrogen-induced abdominal fibroids. But another aspect very relevant from the point of view of neoplastic growth may be mentioned here: this fibroid obeys what may be termed the law of differential behavior of homologous territories of different species or strains, a fact known through the work of many authorities with various tumors, especially in mice. The domesticated guinea pig has been as yet the only species in which we were able to induce uterine and other abdominal or thoracic fibroids. We have

failed with the rat (Egana), the South-American rodent, Octodon degu (Bruzzone, Febres), with the capuchin monkey, cebus apella of Ecuador (Iglesias and Lipschutz, Bruzzone, Awad); other workers failed with the rhesus monkey (Vargas; Engle, *et al.*); and we failed even with the non-domesticated guinea pig, cavia aperea, on which an ample study has been made on behalf of our department in Bolivia itself, the natural habitat of this animal (Iglesias). It is definite that the estrogen-induced abdominal fibroid is bound, like all neoplasms, to a specific and hereditary reactivity of tissues. So fundamental is this fact with these fibroids that there is even a quantitatively different behavior of the abdominal serosa of the two sexes in the guinea pig, a difference which is not dependent upon the gonadal hormones (Lipschutz, Koref, *et al.*). Longer treatment and larger quantities of estrogen are necessary so as to induce fibroids in the male similar to those in the female.

There is still a last aspect I should like to insist upon: atypical epithelial and conjunctive proliferation similar to that elicited with the prolonged administration of estrogens can be elicited in the body with the prolonged action of the animals own ovarian estrogen. Years ago we established that with an operative interference on the ovary endometrial glandular hyperplasia and adenomatous proliferation, glandular invasion of the myometrium, metaplasia and epitheliomatous proliferation of the uterine cervix can be induced (Lipschutz, *et al.*). We then supposed and recently have proved in a clear-cut manner that under these experimental conditions there is an overthrow of the normal ovarian-hypophyseal relationship. Also fibrous nodules on the surface of the spleen similar to those induced by the administration of estrogen can be elicited without administrating the hormone. These nodules appear in experiments with intrasplenic ovarian grafts. The phenomenon is evidently due to the action of estrogen circulating in the spleen before being drained to, and inactivated in, the liver.

Though the phase of autonomous neoplastic growth is not reached with the estrogen-induced abdominal fibroid the above experimental statements give sufficient proof that estrogen-induced atypical growth including the abdominal fibroid is

in some way related to those proliferative processes which lead ultimately to neoplastic growth. It seems thus justified to use the experimental fibroid as a *test* for the study of the antitumorigenic action of steroid compounds.

## Current Studies

Progesterone and androgens have been used as early as 1936 to 1939 by different workers to antagonize the tumorigenic action of estrogens in experiments with estrogen-induced endometrial glandular hyperplasia, and with hyperplasia of the prostatic stroma in experimental animals and in man. There was also some work done with androgenic treatment in cases of uterine fibroids in women.

Clear-cut results were obtained in our work with the antifibromatogenic action of progesterone (Lipschutz, Murillo, and Vargas). Abdominal fibroids failed to appear when this steroid was injected simultaneously with fibromatogenic quantities of estrogen. The preventive action of progesterone was often an incomplete one. There were small nodules on the spleen and the surrounding parts of the stomach and the abdominal wall. These nodules are the first to appear with small doses of estrogen, and they are the last to disappear with the antifibromatogenic action of steroids.

Parting from what was then known about the quantities necessary to antagonize the action of estrogen on the vaginal mucosa in the castrated rat we used at the beginning quantities of progesterone 150 times larger than those of the simultaneously injected estrogen. But the quantitative aspects changed radically when we began using subcutaneously implanted tablets of estrogen and progesterone. Then we found that the quantity of progesterone necessary to prevent estrogen-induced fibroids was not greater and sometimes even smaller than the quantity of the estrogen (Lipschutz, Bruzzone, and Fuenzalida).

In the course of our work we applied with the purpose to express our quantitative results, a diagram giving on the abscissa the quantity of estrogen absorbed per day, and as ordinates the quantity of progesterone. Up to a certain level of progesterone all animals gave fibroids, independently of

the quantity of estrogen absorbed per day. Above a certain level, about 20 mgm. per day in our diagram, most animals were without fibroids. We may add that all these figures are but very approximate as known to those working with subcutaneously implanted tablets.

Antifibromatogenic action can be expressed also in another way. The fibrous reaction of each animal can be given in units according to a system of classification we have adopted. Then the difference between a group of animals with tablets of α-estradiol only, and of animals with tablets of both α-estradiol and progesterone is striking and absolutely convincing.

I have to confess that I was never able to overcome a disagreeable feeling when working with these figures of very doubtful precision. Quantities of 15 or 20 mgm. might as well be 30 or 40. But examples taken at random from our work show how reliable general and comparative conclusions about the antifibromatogenic action are.

Testosterone and desoxycorticosterone, free or esterified, and other steroids of progestational, androgenic and cortical activity were tried subsequently as to their antifibromatogenic activity. Several of them revealed to be active though greater quantities were necessary than with progesterone. Two very relevant questions arose: first, whether antifibromatogenic steroids offer typical structural particularities; and secondly, whether antifibromatogenic activity is related to, and dependent from, the progestational, androgenic or cortical activity of the respective steroids. Progress in our work in the course of the last five years was mainly due to strictly defining and limiting our problems and tasks in the above mentioned double sense.

Making a systematic search between natural or synthetic steroids twenty-three different compounds and five esters of these were examined. Three structural aspects came to prominence in our work.

*First:* All antifibromatogenic steroids have a ketonic group at $C_3$: progesterone, testosterone, desoxycorticosterone, dehydrocorticosterone. On the contrary, all seven steroids with an hydroxyl group at $C_3$ which we examined showed no anti-

fibromatogenic activity even when very considerable quantities were used, as for instance with 21-acetoxypregnenolone; quantities of this steroid almost a hundred times greater than the antifibromatogenic threshold of progesterone were still unable to prevent fibroids (Bruzzone). Though the fibromatogenic action of estrogen is seemingly somewhat diminished with these large quantities of 21-acetoxypregnenolone, none of our experiments with the 3-hydroxyl-compounds was able to shake the statement about the ketonic group at $C_3$ being fundamental for antifibromatogenic activity.

*Second:* The mentioned four antifibromatogenic compounds which occur in the body have a double bond $\triangle^4$ in ring A. We tried then dihydrotestosterone lacking the double bond. a synthetical androgen due to the Ruzicka group. It revealed to be no less, if not more, antifibromatogenic than testosterone.

*Third:* Since progesterone and desoxycorticosterone are more antifibromatogenic than testosterone and dihydrotestosterone (Lipschutz, Nunez, and Vargas) we tried two 3-keto-steroids lacking the double bond at $\triangle^4$ but having a side chain at $C_{17}$—pregnanedione and allo-pregnanedione—with the hope they may be more active than dihydrotestosterone. But contrary to our expectation there was no antifibromatogenic action with quantities several times those of progesterone. We tried also steroid compounds with a side chain longer than in progesterone as cholestenone and methyldehydrocholate (Iglesias, Giral); they did not reveal any activity with quantities about eight and even fifty times greater than those of progesterone.

From the above results one may conclude that for the moment relations between chemical structure and antifibromatogenic activity must not be overemphasized. It seems clear enough that only 3-keto-steroids are antifibromatogenic; but no more than that we know about the problem of chemical structure and antifibromatogenic action.

The second question we have to discuss now is that of a supposed relationship between known and essential physiological actions of steroids, on one hand, and their antifibromatogenic activity on the other hand. We may say beforehand that a systematic research in this field has led us to the rele-

vant knowledge that there is no such relationship. Our experimental findings shall be given here briefly.

There were at the beginning various observations which seemed strongly in favor of the assumption of antifibromatogenic action being related to *progestational* action.

TABLE 1

| Steroid compound | Progestational action mg/I.U. (Selye & Masson, /34) [no action] | Antifibromatogenic µg per day [no action] |
|---|---|---|
| Progesterone | 1 | 15–20 |
| Desoxycorticost.acetate | 10 | 40–90 |
| Dehydrocorticosterone | [6] | 100 |
| Testosterone | 140–200 | 150 (?) |
| Testoster.propionate | 50 | 130 |
| Progesterone | 1 | 15–20 |
| $\triangle^{16}$–progesterone | >100 | [160] |
| Pregnanedione | [50] | [260] |

(?) Active at lower levels also, but we are not sure whether significant.

Antifibromatogenic activity decreases from progesterone to desoxycorticosterone and testosterone, and so also their progestational action. Different steroids of very low progestational action or void of any such action were not antifibromatogenic either; the non-progestational $\triangle^{16}$ dehydroprogesterone, pregnanedione and allo-pregnanedione were found to have no antifibromatogenic activity.

The results were very suggestive. But when a systematic study of this question was made (Lipschutz, Iglesias, Bruzzone, Fuenzalida) it was revealed that progestational and antifibromatogenic actions are not linked one with another. Five derivatives of testosterone and dihydrotestosterone with a substitution at $C_{17}$ by which progestational activity is enhanced were tried.

Though quantitative results with some of these compounds are not yet definite it became clear that antifibromatogenic activity of these compounds was not enhanced and in some cases even diminished when comparing with testosterone or

dihydrotestosterone. Another statement corroborates these findings: the progrestational activity of pregnenolones is similar to that of testosterone but they have no antifibromatogenic action. After all this it is now fully evident that antifibromatogenic and progestational actions are dissociated phenomena.

TABLE 2

| Steroid compound | Progestational action mg/I.U. (Selye & Masson, 34) | Antifibromatogenic μg per day [no action] |
|---|---|---|
| Testosterone | 140–200 | >150 (?) |
| 17-methyl testosterone | 30 | 150 |
| 17-vinyl testosterone | <20 | [>350] (?) |
| 17-ethyl testosterone | ? | [>210] (?) |
| 17-ethinyl testosterone | 10 | >190 |
| Dihydrotestosterone | ? | >110 |
| 17-methyl dihydrotestosterone | * | >110 |
| Androstene-3-17-dione | 140–200 | [570] |

*Similar to 17-methyl testosterone (Klein & Parkes, 34).
?Active at lower levels, but we are not sure whether significant.

Neither was there any link between *masculinizing* and antifibromatogenic activity.

TABLE 3

| Steroid compound | Masculinizing action | | Antifibromatogenic action |
|---|---|---|---|
| | μg per day | length of clitoris mm. | μg per day [no action] |
| Progesterone | 300 | 0 | 15–20 |
| Desoxycorticost.acet. | 200 | 0 | 40–90 |
| Testosterone | 15–20 | 3 | >150 (?) |
| 17-methyl testost. | 47 | 2 | 150 |
| 17-vinyl testost. | 350 | 2 | [>350] (?) |
| 17-ethyl testost. | 210 | 1 | [>210] (?) |
| 17-ethinyl testost. | 300 | 0 | >190 |
| Dihydrotestoster. | 40 | 4 | >110 |
| 17-methyl dihydrotest. | 74 | 2 | >110 |
| Androstene-3-17-dione | 230–570 | 5 | 570 |

Antifibromatogenic quantities of progesterone or desoxycorticosterone, or a multiple of these quantities, had not the slightest masculinizing influence on the clitoris of the female guinea pig. On the other side masculinizing quantities of testosterone and dihydrotestosterone are still beneath the antifibromatogenic threshold. This has been corroborated with five other androgens as methyl-, ethyl-, and vinyl-testosterone, with methyl-dihydrotestosterone and with androstenedione. These statements show conclusively that antifibromatogenic action is in no way inherent to masculinizing activity.

Two *cortical* hormones as desoxycorticosterone and dehydrocorticosterone have been shown to be antifibromatogenic (Lipschutz and Zanartu). But on the other hand, quantities of 21-acetoxy-pregnenolone which are sufficient to maintain alive the suprarenalectomized guinea pig (Bruzzone, Borel, and Schwarz) were still unable to prevent estrogen-induced fibroids (Bruzzone).

TABLE 4

| Steroid compound | Cortical action | | Antifibromatogenic action |
|---|---|---|---|
| | μg per day | survival >9 days % | μg per day [no action] |
| Progesterone | ..... | ..... | 15–20 |
| Desoxycorticost.ac. | 175–525 | 80 | 40–90 |
| 21-Acetoxypregnenol. | 700–1250 | 80 | [1240] |
| Pregnenolone-3-acet. | 733–2625 | 28 | [500] |

Antifibromatogenic activity is a "common denominator" of a number of steroids characterized by their progestational, masculinizing or cortical actions. At the first glance there seems to be also another common activity denominator of these steroids: their *antiestrogenic* activity.

With estrogen the vaginal entrance is maintained open in the castrated guinea pig; with the simultaneous administration of progesterone or desoxycorticosterone subsequent closure is obtained. Estrogen-induced increase of uterine weight also is counteracted by these steroids. The same is true for estrogen-induced uterine bleeding and estrogen-induced necrosis of the

uterine wall when sufficient quantities of the antifibromatogenic steroid are administered. Endometrial glandular hyperplasia and adenomatous growth also were less pronounced under the simultaneous action of the antifibromatogenic steroids, though prevention of epithelial proliferation was much less complete with the quantities used than was prevention of fibroids.

TABLE 5

All animals with α-estradiol

| Antifibromatogenic Steroid | Duration | F.T.E.* average Units of our scale | Uterus gm. | No. of animals Total | Uterine bleeding No. of animals | Uterine necrosis No. of animals |
|---|---|---|---|---|---|---|
| 0 | 2 | 3.0 | 3.7 | 29 | 8 | 8 |
| Progesterone | 2 | 0.5 | 1.9 | 14 | 0 | 0 |
| Desoxyc.-st.ac. | 2 | 0.5 | 1.9 | 17 | 0 | 0 |
| Testosterone propionate | 2 | 1.8 | 2.7 | 18 | 2 | 0 |
| 0 | 3 | 5.1 | 5.7 | 15 | 4 | 3 |
| Progesterone | 3 | 1.4 | 3.0 | 14 | 0 | 3 |

*Fibrous tumoral effect.

Another example is estrogen-induced fibromyoepithelioma of the utricular bed of the male guinea pig. This tumor also was prevented by 3-keto-steroids.

TABLE 6

Prevention of estrogen-induced fibromyoepithelioma

| Estrogen months | Antifibromatogenic steroids months | No. of animals | | With tumors % |
|---|---|---|---|---|
| | | total | with tumors | |
| 3½ to 6 | 0 | 61 | 7 | 11.5 |
| 7 to 11 | 0 | 60 | 25 | 42.0 |
| 7 to 10½ | 6 to 10 | 25 | 0 | 0 |
| 10 to 10½ | 3¼ to 4½ | 37 | 5 | 13.5 |

Notwithstanding all these evident facts there is no possibility of identification of antifibromatogenic and antiestrogenic actions. None of the antifibromatogenic steroids were

able to counteract the growth promoting action of estrogen on the nipples and mammary glands. In experiments with estrogen and testosterone the sebaceous metaplasia of acini of the mammary gland in the guinea pig was seemingly even more pronounced than with estrogen alone (Lipschutz). The estrogen-induced enormous increase of the anterior lobe of the hypophysis in the rat was not prevented by progesterone (Lipschutz, Riesco, and Anfossi).

On a purely experimental basis and without any rationalizing we may conclude that antifibromatogenic activity is not the sequel of any known action inherent to a steroid. It is an antitumoral activity *per se*, which manifests itself in controlling cellular proliferation and differentiation.

What do we know about the mode or site of action of antifibromatogenic steroids? There is no exhaustive knowledge about this question; but certain definite experimental statements can be made. Prevention of estrogen-induced fibroids by certain steroids is not effected by interference in gonadal function or in hypophyseal gonadotrophic function. This is shown in a clear-cut manner by the fact that antifibromatogenic steroids are active against estrogen-induced fibroids in the *castrated* guinea pig. Other possibilities may be suggested: an interference in the enzymatic mechanism of the intrahepatic metabolism of estrogen by which ovarian estrogens are converted into less active urinary ones; an interference in the excretion of estrogens; a desensitizing action in the tissues on which the estrogen acts. In favor of a local desensitizing action is the fact that antitumoral activity of steroids obeys, like the tumorigenic action of estrogens, the law of the differential behavior of homologous territories of different species or strains. The following statement may serve as an example. We have mentioned that as yet we were unable to counteract the estrogen-induced atypical growth of the anterior lobe in the rat with progesterone, in any case with quantities which were the multiple of the antifibromatogenic threshold. Contrary to our findings with progesterone in the rat were those of the Gardner group in mice in which the tumorigenic action of estrogen on the anterior lobe was counteracted with testosterone.

These comparative statements are essential; they show that any generalization of experimental results with the antitumorigenic action of steroids in clinical work would be at variance with the real state of things in the experimental field itself. The task of practical application of experimental findings with the antitumorigenic actions of steroids cannot be an easy one. Progress in treatment can be achieved only with very careful trial in humans. But on the other hand we should like to lay stress on a rather optimistic conclusion which is reached in our experimental work with the antitumorigenic action of steroid hormones: Since antitumorigenic actions of steroids are not simply a sequel of known physiological actions inherent to these compounds there is place for the hope that antitumorigenic steroids having no other pharmacological action may be obtained by chemical synthesis.

It is evident from the above that antitumorigenic action of steroid hormones is based on an antagonistic play of different steroid compounds which is independent from the gonad and the hypophysis. But on the other hand we have recently established that there is also an intrahypophyseal antagonistic play of steroids, a mechanism which offers utmost interest from the point of view of antitumorigenic actions of steroid hormones. If an ovary is grafted into the spleen of a castrated guinea pig, blood follicles but poor luteinization are found till the end of two months. Later on there is a considerable number of corpora lutea and at about ten months luteinization including that of the stroma is so overwhelming that the ovary offers the picture of luteoma (Lipschutz, Ponce de León, Woywood, and Gay). American writers have seen neoplastic reactions in the intrasplenic ovarian graft also in rats (Biskind group), and in mice (Li and Gardner). It is clear that these abnormal ovarian conditions, including the neoplastic reaction, are due to the anterior lobe being freed from the steroid control as has been recently demonstrated by our work. If estrogen is applied to an animal with an intrasplenic graft, premature and considerable luteiniaztion is induced. When progesterone is given simultaneously the luteinizing action of estradiol is counteracted (Lipschutz, Bruzzone, Humerez). It is the same with desoxycorticosterone (Lip-

schutz, Iglesias, Penaranda). One may tentatively suggest that progesterone may serve for the treatment of luteoma; but here again must we suppose that the results will vary according to the species!

I should like to attract attention to another implication of our results with the tumorigenic and antitumorigenic action of steroids which at the first sight may seem quite unexpected. I mean the steroid balance, or steroid homeostasis, as an autodefensive antitumoral device. In the course of the last five years a wealth of data has been accumulated in our work which seem fully to justify this concept. The rhythmic quantitative variation in the production of estrogen may be considered as an essential device against the tumorigenic action of this hormone, with the probable exception of the hereditary mammary adenocarcinoma in mice where even this device fails. The secretion of progesterone, though rhythmic, is another autodefensive antitumoral device (Iglesias, Lipschutz, and Nieto). Rhythmic secretion of both is dependent upon their complicated interaction in the control of the gonadotrophic activity of the hypophysis. Secretion of 3-keto-steroids by the suprarenals also may be considered as an essential part of the system of antitumoral autodefense. It is remarkable that antifibromatogenic quantities of desoxycorticosterone acetate are not yet toxic in the guinea pig; they are unable to produce any changes in the concentration of the chloride, sodium, and potassium in the blood (Alvarez and Fuenzalida); the antifibromatogenic quantities are even smaller than those necessary for the survival of the suprarenalectomized animal (Bruzzone, Borel, and Schwarz).

Not only the hypophysis, the gonads and the suprarenals, but the liver also plays its part in the establishment of the steroid homeostasis. Its inactivating faculty extends not only on estrogens (Segaloff and others) including the urinary ones (Lipschutz, Becker, Mello, and Riesco) but also on 3-keto-steroids as progesterone and desoxycorticosterone (Dosne). Quantitative limitations and functional adjustments of the hepatic cell to the demands in the steroid matabolism have been repeatedly met with in our work (Lipschutz, Acuna, Carrasco, Bruzzone, Quintana, *et al.*).

It seems not a bold hypothesis that neoplastic conditions of the gonads and of the genital tract, including certain types of cancer, may be due to an overthrow of the normal steroid homeostasis due to a failure in some part of the complex mechanism upon which the normal steroid homeostasis relies. This concept is strengthened by many experimental and clinical observations. The following may be quoted here: Our own work with the production of lutein cysts in the ovary by an operative interference on the latter by which an overthrow of the ovarian-hypophyseal relationship is effected; our findings with the luteomatous condition of intrasplenic ovarian grafts and similar findings of American workers; the findings of the Biskind group with the experimental impairment of the liver in rats on a vitamin B free diet; those of Ayre and Bould with uterine cancer in women with thiamine deficiency; those of Wooley and Little with adrenal cancer developing in castrated mice.

Steroids have been shown in our experimental work with tumors to be essential for maintaining cellular proliferation and differentiation at a normal level in the adult body. They have long been shown to be essential for the morphogenic integration throughout the whole life. These results are fully coincident with those of the Needham, Waddington, and Nowinski group with embryonic growth. These authorities have forwarded certain evidence that steroids may well play the role of organizers in embryonic development. On the other hand eminent workers have repeatedly claimed that neoplastic growth is somewhat linked with an embryonic condition of the proliferating tissue though the workers have approached the phenomenon from very different angles. What is now known about the tumorigenic and antitumorigenic actions of steroid hormones and about the part an overthrow of the normal steroid control of cellular proliferation and differentiation may have in neoplastic growth, links the latter anew with the fundamental processes of early development and growth.

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# NOTES ON NEW METHODS IN THE INVESTIGATION OF TYPHUS FEVER

LUDWIK HIRSZFELD*

The observations reported herewith were made during the German occupation of Warsaw in the Stawki Hospital within the Ghetto walls. After the preliminary findings were presented before the meeting of the Medical Society of Warsaw on 15 May 1942, the work was discontinued due to war operations and has been recently resumed in Wroclaw.

*The Technique of Isolation of Proteus X.* For the isolation of Proteus X strains from the blood and urine of typhus fever patients the Mueller-Kaufmann medium containing ox bile was found particularly suitable. Best results were obtained when 1–2 ml. of whole blood of the typhus patient in the second week of disease were inoculated into each tube containing M.K. medium. For each case at least a dozen inoculations should be made. After an incubation of 24–48 hours a transfer is made on nutrient agar. The cultivated strains of Proteus were readily agglutinated with the typhus patients' sera in dilutions 4 times higher as compared with the standard Proteus X 19 strain. In using the above technique a total of 30 Proteus X strains were isolated from the blood, urine, and post-mortem material of typhus fever cases.

*The Uroprecipitation in Typhus Fever.* We have found previously that the sensitization of red cells influences their absorption capacity on filter paper. The principle of this phenomenon was applied to the cultivation of Proteus X. For this purpose typhus patient's serum was added to the patient's urine and filtered. The filter paper was then cut in small parts which were submerged in Mueller-Kaufmann medium. In a large proportion of our tests Proteus X was cultivated.

While this technique was being elaborated a "uroprecipitation" which we further investigated was observed. The test for this phenomenon is: To each of five test tubes of the series 2.5 ml. of urine is added followed by the addition of

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patient's serum in decreasing amounts of 0.5, 0.4, 0.3, 0.2, 0.1, 0.05 ml. After 15 minutes a precipitate is formed in certain dilutions.

This test which originally seemed to be specific for typhus fever proved also positive in typhoid and scarlet fevers. There are cases in which the serum of the patient added to his own urine gives negative results but when urine from another is added the test is positive. If the uroprecipitation indicates a specific substance there might be also another factor of overlapping antigenicity or an appearance in the urine of substance as result of colloidoclasia.

Note: This brief report by Dean Hirszfeld was to have been included in the "Symposium of Polish Medical Contributions in World War II," published in the Summer, 1947, issue of *Texas Reports on Biology and Medicine*. It was unfortunately delayed by circumstances beyond control.

# REVIEW OF COSTEN'S TEMPOROMANDIBULAR JOINT SYNDROME: REPORT OF A TYPICAL CASE*

CECIL GREER AND BEN T. WITHERS

There is a disease entity which is frequently overlooked by otolaryngologists in our part of the country, yet one which is of considerable importance. Formerly believed to be relatively rare and referred to only in dental literature, it is now recognized as a common occurrence of particular concern to the otolaryngologist. It was first adequately described in the literature of our field by Costen of St. Louis. It seems fitting therefore, from the point of view of the otolaryngologist, to refer to it as "Costen's Temporomandibular Joint Syndrome," or more tersely just "Costen's Syndrome."

In describing this symptom complex Costen states: "It occurred in a case of malocclusion and destructive conditions of the mandibular joints and was relieved by proper jaw reposition. It consisted of vertex and occipital pain, otalgia, glossodynia (burning tongue) and pain about the nose and eyes. The ear symptoms were a sense of impaired hearing or stuffy sensation in the ears, tinnitus and grating noises, dizziness relieved by inflation of eustachian tubes and different degrees of ear pain . . . and trismus. The diagnosis . . . depends upon history, gross findings, roentgen study, and test of treatment." More detailed consideration of these matters will be given presently.

A clear understanding of the anatomy of the temporomandibular joint and associated structures is necessary before the abnormal joint function can be appreciated and the attendant symptoms explained. Attention is therefore directed to the following illustrative plates reproduced from Costen's reports. Figure 1 shows from the mesial aspect, the temporomandibular articulation with the position assumed by the articular structures with full molar support. The condyle exerts no appreciable pressure on the meniscus under normal conditions.

*Read before the Ophthalmological and Otolaryngological Section of the Houston Academy of Medicine, October 10, 1947. From the Department of Otolaryngology, Texas Eye and Ear Infirmary, Houston, Texas.

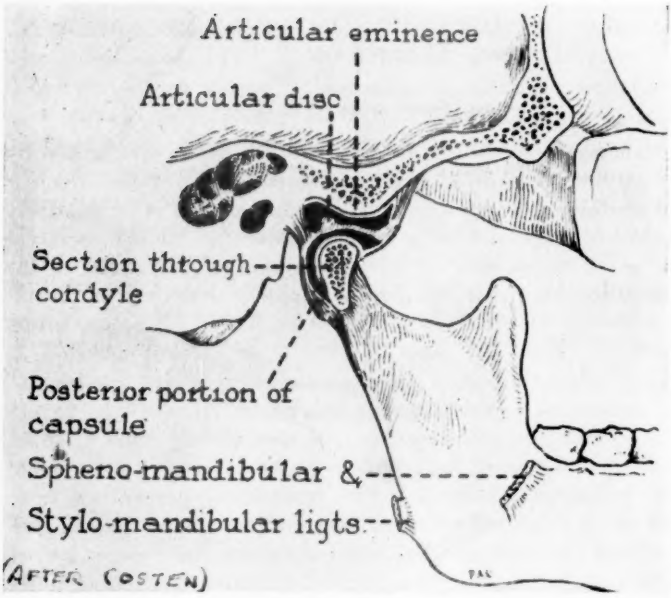



FIG. 1. The temporomandibular articulation. Schematic drawing to show position assumed by articular structures when full molar support is afforded (mesial aspect). No pressure is exerted on the meniscus by the condyle. (After Costen.)

Figure 2 illustrates that the variety of movements is increased in the pathological temporomandibular joint. Lacking molar support the condyle rides upward against the meniscus, forward against the articular eminence or backward against the tympanic plate.

In the next two illustrations pertinent distribution of the Vth Canial nerve is shown. Figure 3 indicates areas supplied by the second and third divisions of the Vth nerve. Reflex pains initiated by irritation of the auriculo-temporal and chorda tympani nerves are expressed in these areas. It is along the course of the lingual nerve that pain in the tongue occurs. Various sensory disturbances arise in the region supplied by the chorda tympani. Figure 4 shows branches of the mandibular nerve; the motor or masticator nerves are shown

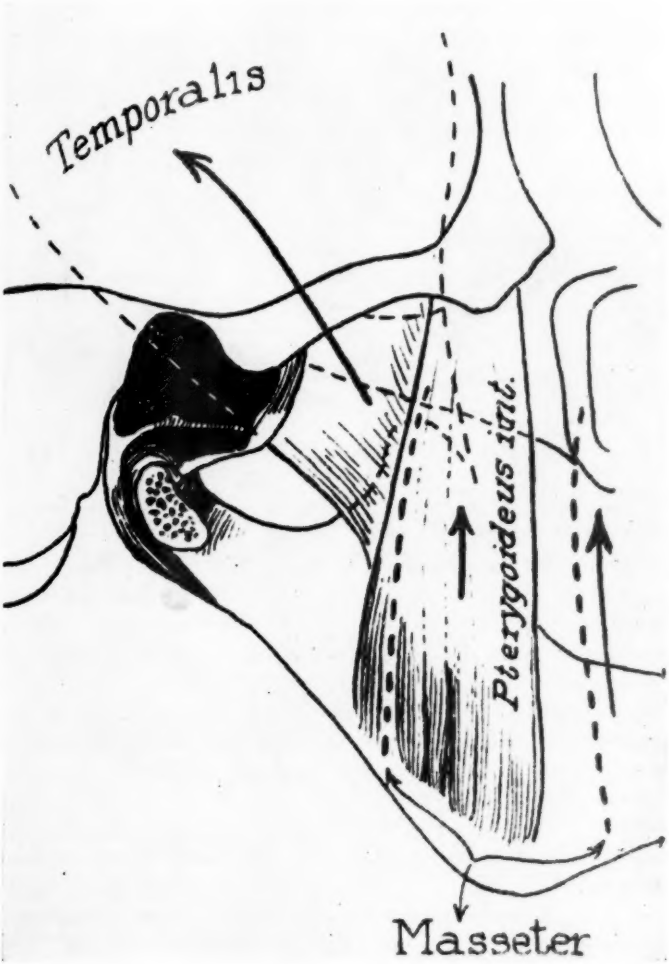



FIG. 2. Variety of movements increased in the pathological temporomandibular joint. With molar support gone, condyle is brought upward against meniscus, forward against articular eminence, or backward against tympanic plate. (After Costen.)

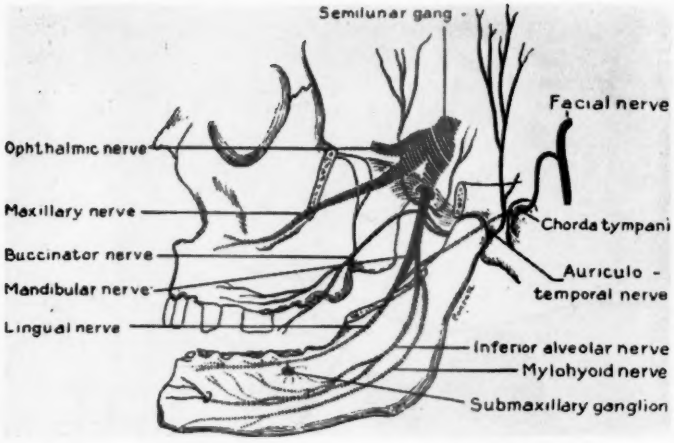



FIG. 3. Schema to show the various areas supplied by the fifth nerve. Reflex pains initiated by irritation of the auriculotemporal and chorda tympani nerves are expressed in these areas. Pain in the tongue occurs along the course of the lingual nerve. Various sensory disturbances arise in the region supplied by the chorda tympani. (After Costen.)

in black and the sensory branches in white. Sensory irritation from structures in this area as from inflammation of the parotid glands, ramus of the jaw or pharyngeal tissues, produces trismus by contraction of the powerful masticator muscle.

In addition to the above-mentioned facts concerning the anatomy, it should be borne in mind that the epipharyngeal orifice of the eustachian tube is in close relation with the temporomandibular joint medially.

Having thus reviewed the anatomy, it remains to consider briefly the etiology, pathogenesis, diagnosis, treatment and prognosis of Costen's Syndrome and to present one typical case from our own practice. The etiology and pathogenesis are so interrelated that they may be discussed together. The pressure upon, and anatomical distortion of, the joint and adjacent structures is dependent on actual destructive changes. The destructive changes in the temporomandibular joint are brought about by undue and unnatural pressure on the meniscus, glenoid fossa and condyle or head of the mandible. Such

pressure may be of a type due to acute or chronic trismus, *i.e.*, "The tonic contraction of the muscles of mastication." In the chronic trismus group, the usual finding is that complete loss of molar teeth and hence molar support invites destruction of the mandibular joints. However the paradox is frequently seen in a person with no molar teeth at all and yet no evidence of joint changes.

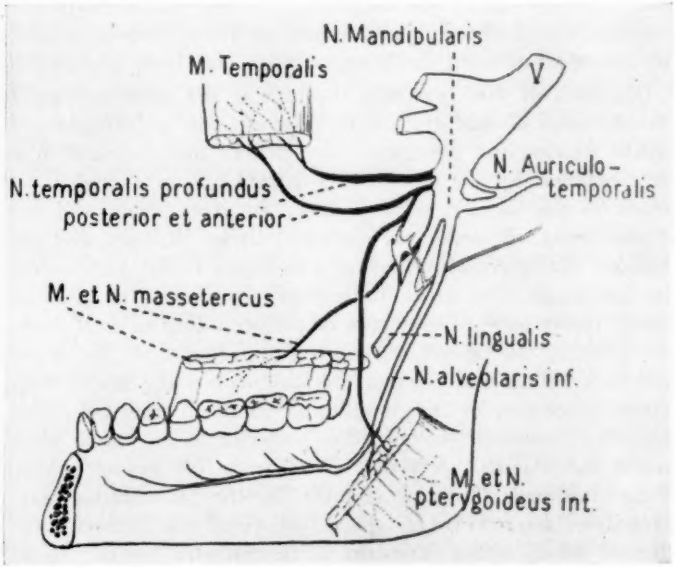



FIG. 4. Schema showing branches of mandibular nerve, the motor or masticator nerves shown in black and sensory branches in white. Sensory irritation from all structures in this district, as from inflammation of the parotid gland, ramus of the jaw or pharyngeal tissues, produces trismus by contraction of the powerful masticator muscles. Relaxation of various grades of trismus in these studies by simple movement of the condyles away from the auriculo-temporal nerve and its sensory branches suggests that irritation by the impacted or abnormally impinged condyle is the mechanism of continuing the trismus. (After Costen.)

Among the causes of acute and chronic trismus, Costen lists the following from his case histories: yawning, biting of an apple, blow on the chin, stretching of jaws under anesthesia, ulcerated tooth, peritonsillar abscess, parotitis, psychoneurosis, fracture of the jaw, furuncle of the ear, tetany,

tetanus, ill-fitting dental plates, impacted unerupted teeth, malocclusion, and habit of removing dentures. In Figures 3 and 4 above, the mechanism of the production of trismus was demonstrated to be a reflex phenomenon. It may be compared to the board-like abdomen resulting from intense peritoneal irritation. Other symptoms such as otalgia, glossodynia, stuffy feeling in the ear, and conductive deafness are readily explained if one recalls the anatomy. Pressure on the auriculotemporal nerve, chorda tympani and mouth of eustacean tube, in close relation with the joint, accounts for these symptoms.

Diagnosis of this symptom complex is the most important consideration of this discussion. Therein the otolaryngologist fulfills his greatest service to the patient and prepares him for treatment by the dentist. As quoted above, diagnosis depends on the history, gross findings, roentgen study and test of treatment. History was discussed under etiology and pathology. As to gross findings and roentgen study, Costen lists the following: first, gross findings are "unilateral or bilateral loss of molar teeth, overclosure or malocclusion natural teeth, or ill-fitting dental plates, uneven movement of the lower jaw on opening and closing, crepitus within the mandibular joints, tenderness of the mandibular joints to internal palpation (*i.e.*, index finger palpation posterior to last molar teeth inside the mouth) presence of trismus, all grades"; then X-ray findings: "density changes in the mandibular joint structures, narrowing of spaces between the condyle and glenoid fossa, either uniform or asymmetric, widening of joint spaces and wide excursion of the condyles in the open position, fixation of one condyle against the tubercle and normal excursion of the opposite condyle, erosion of the anterior surface of the condyle and posterior aspect of the articular tubercle, change in normal contour of glenoid fossa (deepening) and of the condyle, but with normal bone surfaces (suggestive of abnormal stress), fracture of the tympanic plate, impacted unerupted third molar teeth."

Details of the X-ray technique will not be discussed here but are available in an article by Ernst and Costen. The technique is not difficult and is adaptable to any standard X-ray machine suitable for sinus and mastoid studies. Illustrations

of some of the roentgenological findings will be presented in connection with the case report.

The test of treatment is important not only in establishing the diagnosis but in giving the patient a preview of the comfort and freedom from symptoms to be gained by correction of the basic pathology. Obviously, removal of the abscessed teeth, impacted teeth and correction of similar causes of trismus will relieve symptoms. However, the dramatic test of treatment comes in patients whose joint pathology has resulted from lack of molar support. The bite is opened by the use of cork discs of accurate uniform thickness in the molar area or later on by temporary dental appliques. The cork discs are inserted into the molar area by the patient and tested in place while an elastic headgear is applied to fix the jaw. The patient keeps a diary and by trial and error arrives at the correct number of discs necessary to relieve the symptoms. In some cases the discs are required on both sides; in others only on one side.

To help relieve the trismus and also give the patient much-needed rest, small doses of phenobarbital are given over the trial and error period when the patient is keeping his diary. When the number of discs required to relieve the symptoms is decided, then the patient is ready for referral to the dentist. Since the thickness of the discs is known (usually 2 mm.) a fairly accurate measurement can be calculated for the dentist. However at best this is only a starting point for him, and various other more accurate dental measurements will be made by him. The important thing, however, is that the diagnosis has been established and corrective measures are possible, as proven by the test of treatment.

As for treatment of Costen's syndrome, the otolaryngologist is only passively concerned. Dental literature is replete with suggestions on this problem and detailed consideration is not indicated in the scope of this discussion.

The prognosis depends entirely on whether or not the patient is coöperative to the point of establishing the diagnosis, and then following up with the dental correction. Usually, if the patient does not coöperate on the keeping of a diary concerning trial and error use of the discs for molar support, then one

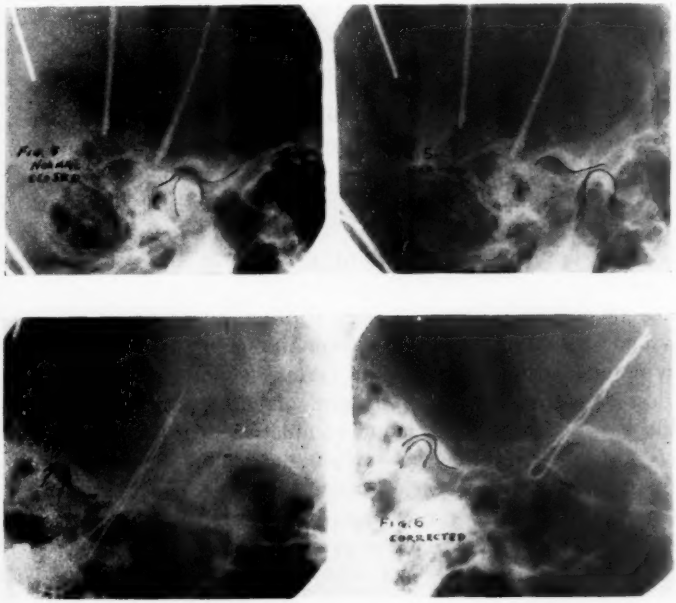
can be sure that the patient is not having the type and severity of symptoms to merit referral to the dentist. If no corrective measures be instituted in a proven case of this symptom complex the pathological joint changes will progress, as will the symptoms.

## Case History

The illustrative case is that of Mrs. D.W.H., white, middle-aged female, who came to the office complaining of pain and stuffy feeling about the left ear, grating in the left jaw joint on movement, and occasional inability to open the jaw because of locking. On these occasions the mouth could finally be opened, but only after prolonged effort and considerable pain on the left side. There was no history of glossodynia or deafness. The patient had upper and lower complete dentures which she had been wearing for six years. Her symptoms had been noticeable for the past year but had been severe only for the past two months. Ear, nose, and throat examination was negative except for the following: patient was completely edentulous; there was marked pain to pressure inside the mouth along the ramus of the mandible on the left; there was palpable crepitus in the left mandibular joint on movement of the jaw. For the test of treatment the patient used the cork discs and small doses of elixir of phenobarbital daily. It was not convenient for her to use the elastic headband, but in her case it was not necessary to relieve the trismus, pain, and other symptoms, because she found relief by using two discs on each side and maintaining a closed position of the mandible. Thus she secured a 4 mm. opening of the bite in the molar area. After referral to the dentist and study by him, it was found by his more accurate measurements that the bite had to be opened 5 mm. Thus our figure of 4 mm. gave him a starting point, and yet was not too grossly inaccurate. Since new dentures were made and the patient has been wearing them she has been symptom-free.

In Figures 5 and 6 X-ray findings are shown. Figure 5 represents the appearance of the normal temporomandibular joint in the open and closed positions of the jaw. The X ray is of a left joint. In the closed position the meniscus is intact

as represented by the smooth even space between the condyle or head of the mandible and the glenoid fossa. The fossa is of normal depth and is not eroded or deepened. The condyle is smooth, rounded and not angulated. In the open position the condyle is slightly anterior to the tubercle, but has neither an extremely anterior excursion nor an extremely posterior excursion.




In Figure 6 are shown the pathological left temporomandibular joint of the patient on the left of the figure in the closed position, and on the right of the figure the same joint in the closed position with the corrected dentures in place so as to re-establish the normal anatomic relations in the joint, or at least to approach the normal sufficiently to stop the symptoms. The open position of the jaw is not shown since this view appeared normal as to position of the condyle in relation to the tubercle. In the view to the left of the figure the meniscus has been worn through until the condyle is

resting directly against the inferior aspect of the glenoid fossa. The condyle is somewhat angulated by erosion. These anatomical changes explain the crepitus within the joint on motion. The right half of the figure shows the relations within the joint with the corrected dentures in place. The outstanding thing to be noted is that with the proper molar support the distance between the condyle and the glenoid fossa has been restored and that in this closed position, the condyle does not impinge on the fossa.

## Summary

Pathological temporomandibular joints had been considered strictly a dental problem until Costen described the otolaryngological implications, the etiology, pathology, and diagnosis. Treatment of Costen's Syndrome still rests with the dentist. The anatomy of the joint is such that the motor and sensory branches of the third division of the Vth cranial nerve, the chorda tympani nerve and the epipharyngeal orifice of the eustacean tube are intimately related. Trismus, malocclusion and destructive conditions of the joint cause symptoms such as pain in the vertex, frontal area or occiput, glossodynia, crepitus in the joint, otalgia, stuffy sensation in the ear, tinnitus aurium and conductive deafness. Diagnosis of Costen's Syndrome depends on the history, gross findings, roentgen study and test of treatment; whereas prognosis depends on whether or not causative factors are corrected. As an example, a typical case is presented.

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We express our appreciation to Dr. James B. Costen of St. Louis for his kind permission to reproduce the anatomical plates, and to Dr. R. S. Harman of Houston, the dentist who is associated with us.

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# CONCERNING THE ORGANIZATION OF THE CEREBRAL CORTEX*

PERCIVAL BAILEY

The cerebral cortex develops by evagination and elaboration of the lateral walls of the endbrain. The earliest evaginations become the olfactory bulbs. At the bases of the olfactory bulbs lies a complex second olfactory area which is invaded and expanded by various nonolfactory systems and this correlation tissue is evaginated and elaborated to form the cerebral hemispheres. The gray matter covering the latter is called the cortex or pallium. The older olfactory portion—archipallium, allocortex—is later pushed to the periphery and completely overshadowed by the vast expansion of the neopallium, called the isocortex because at some time in its ontogenetic development it has a typical six-layered structure. This thin sheet of correlation tissue seems well adapted to the labile type of behavior which we call intelligent, and capable of indefinite expansion (Herrick, '21).

There has been no lack of appreciation of the fundamental importance of the cerebral cortex. Its tremendous increase in size in relation to the rest of the organism, as we ascend the phylogenetic scale, was evident to the early naturalists, but our knowledge of its structure has so far been very rudimentary. A glance into any textbook of neuroanatomy will reveal the contrast between the specific and detailed statements concerning the fiber-tracts and connections of the neuraxis and the vague general terms used to describe the cerebral hemispheres. Cornelis Winckler progressed systematically through the five volumes of his functional anatomy of the nervous system until he reached the cerebral cortex and then balked with the statement that he did not believe himself capable of undertaking the enormous task of elucidating its structure. The early anatomists depended upon dissection and their naked eyes, or a small magnifying glass,

*The James Greenwood Lecture, The University of Texas Medical Branch, Galveston, October 16, 1947. From the Department of Neurology, and Neurological Surgery, University of Illinois Medical School, Chicago.

to disclose the structure of the central nervous system. In this way they obtained only the vaguest conceptions of long fiber tracts which were named the fasciculus longitudinalis superior, inferior and the like. The fact that drawings of these dissections are still reproduced in our texts is evidence that our knowledge has not progressed far. The climax of this approach to the problem was the monograph of Rosett ('33), who tried to perfect a method of exploding the brain so as to separate the fibers and make them more clearly visible. The result of these studies never produced any improvement on the vague diagrammatic illustration drawn by Meynert in 1872 (Fig. 1).

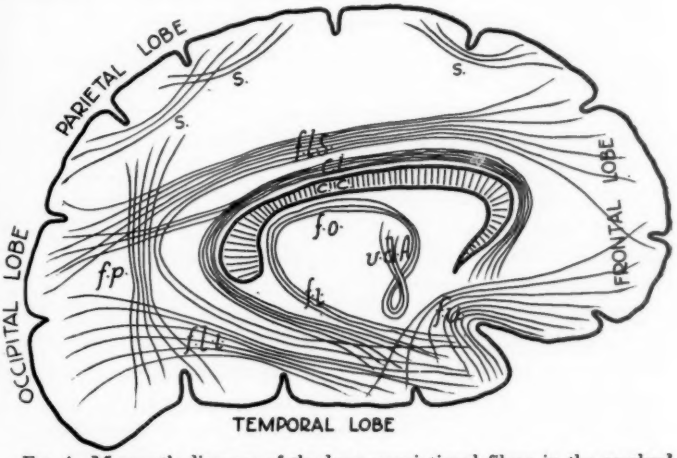


FIG. 1. Meynert's diagram of the long associational fibers in the cerebral hemisphere.

The perfection of methods of staining gave rise to renewed hopes. It was found that many nervous fibers were surrounded by sheaths of myelin which could be sharply and differentially stained by the method of Weigert or its numerous modifications. Since not all fibers were myelinated, patterns appeared which enabled the observer to recognize the presence or absence of certain tracts. It was further found that these sheaths would degenerate if the fiber were detached from its cell of origin and, in so doing, be transformed into neutral fat which

could be again sharply and differentially stained (method of Marchi) so that the degenerating fibers could be followed even when not congregated into definite bundles. By means of these two methods a vast amount of laborious investigation was undertaken culminating, so far as the cerebral hemispheres were concerned, in the two volumes of Dejerine (1895). The results for our knowledge of the cerebral cortex were, however, disappointing. The complication of structure made the Weigert method of little use and even the Marchi method, for the same reason and because so many of the fibers were unmyelinated, gave results incommensurate with the vast labor involved. Such studies have been almost abandoned although the Marchi method continues to be applied to the brains of smaller animals.

The foregoing studies were undertaken because it was believed that the function of various parts of the cortex would be indicated if connections could be demonstrated with other parts of known function. Meanwhile another approach was being cultivated.

It had been noted in 1782 by Gennari, an Italian medical student, that a white stripe could be seen in the middle of the cortex of the occipital region. This stria Gennari was later emphasized by Vicq d'Azyr and its recognition led to the search for other differences in structure of the cortex. The climax of this approach was reached in the study of Elliot Smith ('07) who drew a complicated map of the cortex in which he distinguished many areas whose structure he claimed could be recognized with a simple hand-lens. The search for these areas was stimulated by the belief that the difference in structure meant a difference in function, a hypothesis elaborated by Meynert and expressed by Hughlings Jackson in the following words:

"Differentiation of function implies differentiation of structure and differentiation of structure means differentiation of function. So far as the comparative anatomist detects homological cerebral structures, so far, it is hoped, will the physiologist be able to develop the homological functions, and so far as the anatomist ascertains different structures, so far will the physiologist be able to detect different functions."

As soon as staining methods were applied to the cortex further data were added. Baillarger had noted the six fundamental layers of the cortex which were now more clearly demonstrated by the Weigert method (Fig. 2) and Betz

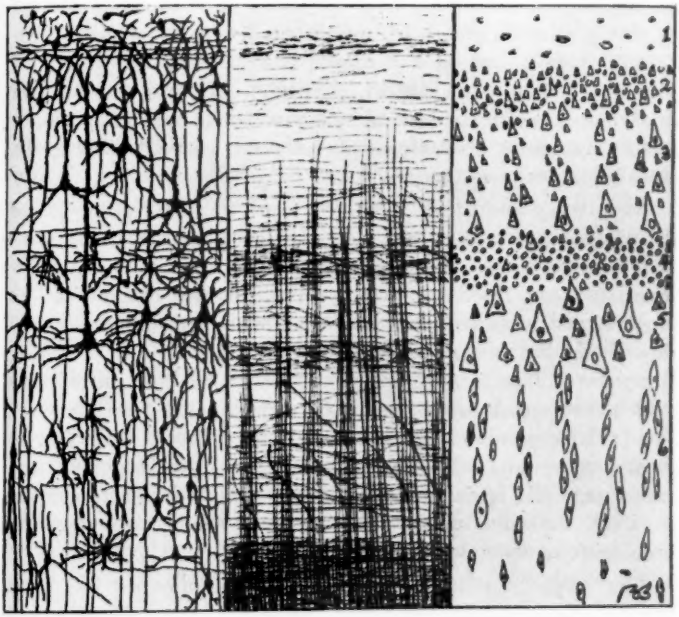


FIG. 2. Diagrammatic representation of the six fundamental layers of the cerebral cortex as they appear by the Golgi, Weigert and Nissl methods.

found the giant cells in the precentral region which bear his name. These studies were continued by Campbell, Brodmann and others and culminated in the studies of O. Vogt, Economo ('29) and their schools. These studies also have proved disappointing since they reveal less than was hoped and have reached a complexity which makes them well-nigh incomprehensible. Recently the revolt against the endless process of parcellation of the cortex has been gaining recruits (Lashley and Clark, Bonin and Bailey, '47). The adherents of the Vogt school maintain that it is their task to describe the facts regardless of any possible significance. This process, however,

leads to that sterile fact-finding against which Robert Hutchins ('36) has been crusading for many years. Long ago Bichat wrote that an anatomy without physiology is an anatomy without purpose. As a matter of fact, every cubic millimeter of the cerebral cortex differs from every other and the attempt to describe each one leads to an endless task without conceptual result, just as the description of each inhabitant of the city of Galveston would leave one still with the task of analyzing the information in terms of some purpose. Science has many means of attaining its purposes without such sterile multiplication of data.

As Lashley and Clark ('46) point out, the descriptions given by writers on cytoarchitectonics of the cortex are often mere paraphrases of each other in which any distinguishing characteristics are absent or buried. The favorite method of the Vogt school is to compare one area with the one previously described, that one with the next adjacent and so on. Aside from the difficulties of describing in words the differences which distinguish areas essentially similar (the word "etwas" recurs with maddening monotony) the process leads to no clear conceptions which would enable one to recognize any given area. It is easy to see, if the areas were arranged in a circle, that one might proceed around and pass the first area without ever recognizing it.

The hypothesis which underlies the studies of the Vogt school is that the cortex consists of a group of organs, arranged in a mosaic with sharp (haarscharf) boundaries between them. These areas were first worked out by Vogt using the Weigert method. Brodmann, using the Nissl method, found the areas recognizable by the latter method not to coincide with those seen with the Weigert method. He left the Vogt laboratory and for years went from one asylum to another without facilities to continue his work and finally died without having been able to publish the data on which his famous map (Brodmann, '08) of the cerebral cortex reposed. All subsequent pupils of the Vogt school have found that the results of the Nissl method agree admirably with those of the Weigert method (Strassburger, Nyowgang, Gerhardt). As a matter of fact, if one accepts the parcellation revealed by the Weigert method,

it is possible to describe peculiarities of the Nissl picture in the same areas but the result will be essentially meaningless.

This makes it necessary to scrutinize carefully the results of the Weigert method. It takes only a brief experience to convince one that it cannot deliver constant and reliable results. Slight variations in differentiation of the sections change radically the appearance of the area. Vogt knows this (Fig. 3) but tries to minimize the difficulty. When we read, however, in Strassburger ('37) that the sections were retouched with a camel-hair brush until the desired structure was visible we lost all patience, discarded the Vogt scheme and have since depended more on the Nissl method.

What does the method of Nissl (or its many modifications) show us? It gives a very incomplete but constant picture. The cells may be more or less easy to see but they are all there and we soon become convinced that vast areas of the cerebral cortex resemble each other so closely that it is impossible to describe in words their differences so clearly as to enable one to recognize them. If differentiation in structure means differentiation in function then the converse is also probably true and one must conclude that vast areas of the cerebral cortex must have an essentially similar function. This does not mean, of course, that they may not have other functions. Railroad systems have in common the function of transportation but the results of their functioning may be quite different. Depending on their connections one line might transport coal and support a manufacturing district whereas another might transport grain and be essential as an outlet for an agricultural district. A bomb dropped on a great depot of the first line would derange the function of manufacturing whereas the result of an injury to a depot of the latter would be felt first in the function of agriculture even though both depots were structurally identical.

Winckler ('39) put the matter succinctly when he wrote: "I am convinced that these researches aim at a false goal. In my opinion it is impossible to determine cortical areas, of which the number has increased alarmingly, exclusively by their cellular structure. Besides their cellular structure one must examine their fibrillary structure, their reciprocal

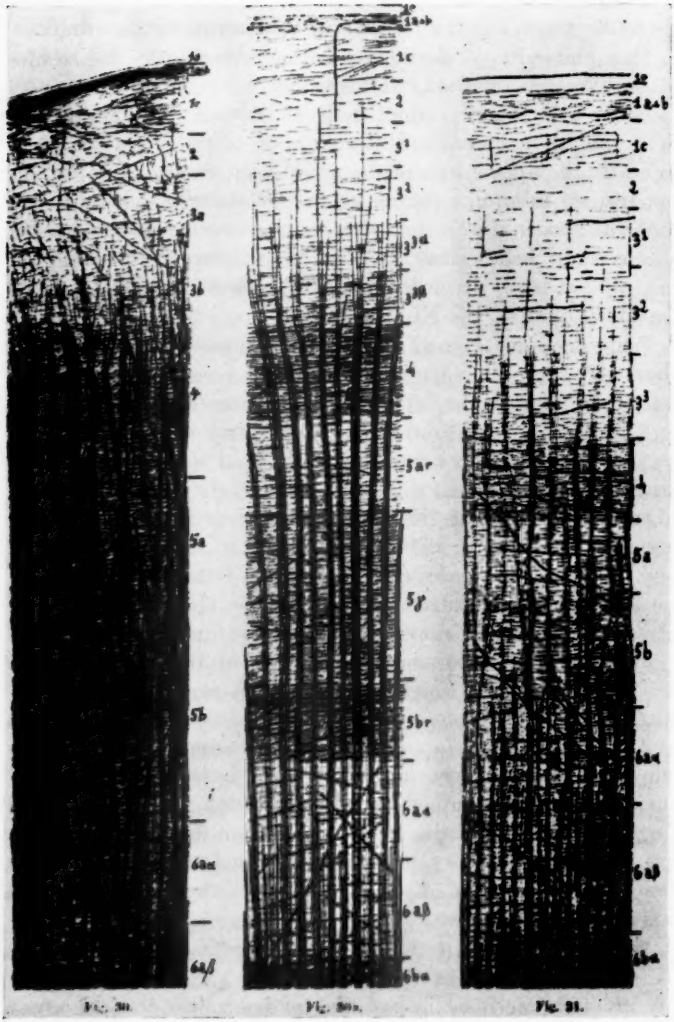

FIG. 3. From C. and O. Vogt. Figures 30 and 30a are from the same area but 30a has been further differentiated. One wonders whether Figure 31 has not also been overdifferentiated.

relations, and the alterations which they undergo after partial or total section of the corona radiata or after ablation of other parts of the cortex." One must be careful, therefore, not to expect too much of the Nissl method. Too sweeping conclusions cannot be drawn from its incomplete revelations. The results of other histological methods must be utilized (Lorente de No, '43).

Lately the problem has been attacked by newer technics. The development of radio engineering has made it possible to amplify very small variations of electrical potential so that they can be recorded. It has been possible to map accurately by the use of these methods the areas of termination of the somesthetic impulses in the cortex (Marshall, Woolsey, and Bard, '37), the auditory impulses (Ades and Felder, '45), the visual impulses (Kornmueller, '37) and to discover second areas for each of these systems hitherto unsuspected (Woolsey, '47).

Since Berger in 1929 proved that such variations of voltage occur spontaneously in the cerebral cortex, Kornmueller ('37) believed that he could detect a difference in the electrical activity of each histologically distinguishable area of the cortex. The method is certainly not capable of doing this, at least through the intact skull, but has been useful in other ways. As an example we may describe the one most widely adopted and called by Dusser de Barenne "physiological neuronography." When a small bit of filter paper, soaked in a saturated solution of strychnine sulphate, is placed on the surface of the cerebral cortex the electrical discharges of its neighboring cells are synchronized, producing large voltages known as "strychnine spikes" which are transmitted over the axones coming from those neurones and may be detected by electrodes situated in the regions in which those axones end. Although no information is obtained concerning the course of the fibers a great deal of accurate information can, and has, been obtained in this way about the interrelations between various regions of the cerebral cortex and about their relations with the basal ganglia, mostly by Dusser de Barenne and his pupils. This information is precious. The older methods had revealed no connections of the cortex with the basal

ganglia because the fibers involved were unmyelinated. In the cortex also the older histological methods had yielded few and dubious results because the fibers were not myelinated all the way to their terminations, and also because they were too scattered, in an inextricable tangle, to make possible an analysis by methods of axonal impregnation.

We should also note the results obtained by another experimental histological method known as Gudden's. Gudden found, when an axone was severed from its cell body, not only that the axone degenerated but also that the cell-body was severely damaged and might disappear. A great deal has been learned about the origin of many fiber tracts by the method but it has never been of much use in investigating the cortex because the intricacy of structure makes reading of the results too uncertain. It has, however, in the hands of d'Hollander, Le-Gros Clark, Walker and others, given a lot of very exact information concerning the relations between the cortex and the thalamus. Since the functioning of the cortex depends not only on its internal structure but also on its connections, this information must be used in any attempt to formulate an account of the functional organization of that organ.

Embryology added its bit to the accumulating data. Flechsig found that different areas of the cortex acquired their myelin sheaths at various periods of development, in a definite order which has interesting correlations with their probable functions. This work has recently been confirmed by Chr. Jakob ('43).

If we try now to correlate all these sources of information, let us see whether we can gain any clear ideas concerning the organization and functioning of the cerebral cortex.

In the beginning we must recognize the distinction drawn long ago by the comparative neurologists between the phylogenetically older and newer cortex or, as they are now called, the allocortex and the isocortex. The allocortex is closely connected with the olfactory system and has a fundamentally different internal structure. It is out of this older cortex that the isocortex differentiates. Between them is a zone of intermediate structure, sometimes called the mesocortex, of which that covering the cingulate gyrus is a good example. In the

macaque monkey most of the cortex of the frontal lobe bears traces of its olfactory origin but, in the chimpanzee and man, these are lost except around the margin adjacent to the allocortex. We know little about the functions of the allocortex except by inference from its connections because it is so buried in higher mammals as to make experimental investigation very difficult. We shall, therefore, be concerned herein largely with the isocortex. In the following discussion the reader should consult the map of the cortex drawn by Economo (Figs. 4a, b).

The typical isocortex (Fig. 2) consists of six layers, from without inward as follows: (1) the molecular layer containing few neurones, (2) the outer granular layer, (3) the external layer of pyramidal cells, (4) the inner granular layer, (5) the internal layer of pyramidal cells and, (6) the layer of fusiform cells.

The portion of the isocortex which comes, when fully developed, to have a structure most widely at variance with the general pattern is that portion around the calcarine fissure of the occipital lobe which we know as the striate cortex (OC). It is recognizable even with the naked eye, as Gennari noted, by the prominent white stripe in the gray mantle. Anteriorly it is buried in the fissure but posteriorly spreads out over the surface at the tip of the lobe in man. In the macaque and chimpanzee it covers a wide expanse also on the lateral surface. It has a sharp boundary, readily recognized under the microscope. On the lateral surface of the brain of monkeys and apes this boundary lies just posterior to a deep fissure called the simian or lunate, which is very small or absent in man. The striate cortex corresponds exactly to the area of projection of the lateral geniculate body which transmits visual impulses from the retina (Kornmueller, '37). There is a point-to-point correspondence between the retina and the striate cortex, the details of which we do not need here to mention (Polyak, '32). It is to the striate cortex, therefore, that visual impulses arrive and destructive lesions within it cause definite defects in the visual fields. For the various implications of this fact you should consult volume VII of the Biological Symposia ('42).

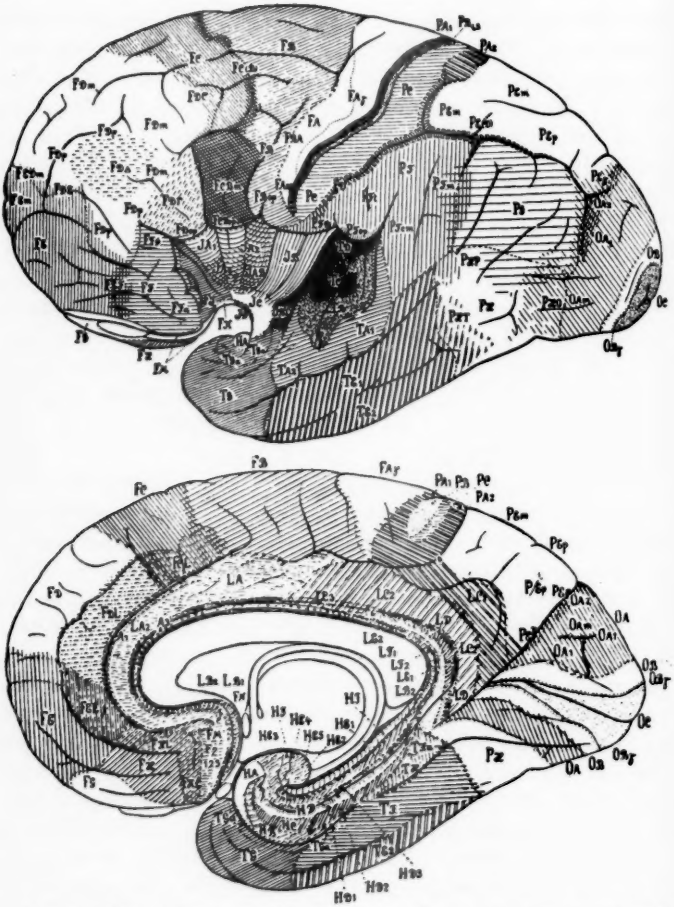

FIG. 4. Map of the cerebral cortex according to Economo; *a*—lateral surface; *b*—medial surface.

Immediately surrounding the striate cortex is typical six-layered isocortex, known as the parastriate cortex (OB). This cortex is thin, especially the fifth and sixth layers, and the fifth layer is largely empty of cells. It receives fibers from the striate cortex and sends fibers to the cortex immediately anterior to itself and to the cortex of the opposite

hemisphere through the splenium of the corpus callosum. It is obviously under the influence of the striate cortex and what little we know of the effects of destructive lesions in this area indicates that it serves to elaborate and correlate visual impulses before transmitting them to the adjacent peristriate cortex. Destructive lesions of it disturb the recognition of objects and pictures (Nielsen, '46).

The peristriate cortex (OA) lies around the parastriate cortex. Its boundaries are obscure. As one passes from the margin of the striate cortex anteriorly the cortex slowly thickens, the large cells of the deeper part of the third layer become smaller, and the radiations finer. We may take as characteristic of it the cortex lying just anterior to the lunate sulcus. There is no definite boundary visible under the microscope between it and the parastriate cortex but its connections seem to be quite different. It receives fibers from the parastriate cortex and also from the pulvinar of the thalamus (Walker, '38) and sends fibers widely to the cortex anterior to itself, even well within the frontal lobe (Chusid, Sugar, French, '48). We find ourselves now within the great correlation tissue which subserves the intrinsic function of the cortex. This portion is intimately related to visual functions and destructive lesions within it disturb the revisualization of former images (Nielsen, '46).

The striate cortex is a very granular cortex, called by Economo *koniocortex*. Wherever there is a primary projection of sensory impulses to the cortex it tends to approach this type. Another example lies around the splenium of the corpus callosum within the allocortex. This retrosplenial area (LE) probably has to do with olfaction.

Within the isocortex we may recognize also the postcentral koniocortex (PB) in the posterior wall of the central sulcus. Marshall, Woolsey, and Bard ('37) have proven that tactile impulses from the hairs of the skin project to this area whose third layer contains mostly granules with a few interspersed long slender pyramidal cells. Its fifth layer is thin, pale, and relatively poor in cells. The primary somesthetic projection is not, however, confined to this postcentral granular cortex but spreads out over the entire postcentral ascending

gyrus which, aside from its anterior wall, is covered by six-layered cortex (PC + PD) which varies little from the general pattern of the isocortex. It contains some very large pyramidal cells in the deeper regions of the third layer and its fifth layer is relatively empty of cells. All of this postcentral cortex, which extends over onto the medial surface of the hemisphere, receives somesthetic impulses transmitted via the posterior ventral nucleus of the thalamus (Walker, '38). Destructive lesions of the postcentral ascending gyrus cause defects of cutaneous sensation on the opposite half of the body in definite orderly sequence (Athanasiu-Benisti, '18).

Behind the primary somesthetic area the cortex thickens on both sides of the intraparietal sulcus to become typical six-layered isocortex. It varies little in the remainder of the parietal region. Above the sulcus (PE) the fifth layer is relatively empty; below the sulcus the cells of the fifth layer are more numerous and are somewhat larger in the supramarginal gyrus (PF) than in the angular gyrus (PG). The angular area adjoins the peristriate cortex without any definite boundary. This vast parietal associative area has connections with posterior lateral nucleus and pulvinar of the thalamus (Walker, '38), with the homologous areas of the opposite hemisphere, and sends fibers widely into the frontal, temporal and occipital associative areas (Bonin and Bailey, '47).

Destructive lesions of the superior and inferior parietal lobules cause disturbances of functions which depend mainly on correlation of visual and somesthetic sensory data, such as astereognosis, apraxia, anosognosia, other disturbances of the body scheme, and alexia if the left angular gyrus is involved (Nielsen, '46).

Another koniocortex (TC) lies on the supratemporal plane, covering what are known as Heschl's gyri. It is a granulous cortex, only a few small pyramids remaining in the third layer. The small cells are arranged in small columns which gives this cortex what Economo called a "rain-shower" appearance; the fifth layer is again very poor in cells. This koniocortex occurs in patchy distribution within an area (TB) which has larger cells in the deeper parts of the third layer.

It has been proven that this is the auditory receptive area by electronic recording (Ades and Felder, '45). The impulses are transmitted from the cochlea by way of the medial geniculate body. Fibers go from the primary auditory area to the frontal lobe (Sugar, French, Chusid, '48) for correlation with movements of the eyes and of the speech-musculature and to the surrounding portions of the temporal lobes (TB, TA, TE).

Around the primary auditory cortex one finds much the same series of changes that occur about the primary visual and somesthetic receptive areas. About each is a zone containing big cells in the deeper part of the third layer. It is unfortunate that Economo labeled these areas with the letter B (OB, TB) in the occipital and temporal lobes and with a C (PC) in the parietal lobe.

The remainder of the temporal lobe is covered by six-layered isocortex which varies little from the general pattern for the associative areas. Over the outer surface of the first temporal convolution (TA) the cortex looks much like that of the parietal region. So also does the cortex across the base of all the temporal convolutions toward the occipital lobe, in fact so much so that Economo labels it PH. The cortex over the fusiform gyrus (TF) is almost identical. The cortex over the tip of the lobe (TG) is very thick and the cells of the second layer tend to be grouped, reminding one of the proximity of the allocortex. Only over the second and third temporal (TE) gyri is the cortex very distinctive. Here the third layer is thin and poor in cells and the cell columns are unusually widely separated.

The supratemporal plane, the pole, and the second temporal gyrus connect with the homologous areas in the opposite hemisphere; the second temporal gyrus through the anterior commissure. We know nothing of the connections of the basal surface of the temporal lobe. The auditory and para-auditory cortex connects with the frontal lobe in the "eye" field, with Broca's area and with the para- and peristriate cortex. The first temporal gyrus (TA) connects with the primary auditory cortex (TC), with the frontal pole (FE) and with the parietal operculum (PFD). The proper

temporal cortex (TE) has connections with the para- and peristriate cortex and with the periauditory cortex (TA). The pole of the temporal lobe has connections with the orbital surface of the frontal lobe (FF) by way of the uncinate fasciculus. The posterior portion of the temporal lobe (PH in man) is connected with the inferior parietal lobule (PG) the peristriate cortex (OA) and the inferior part of the frontal lobe (FDp).

Except for the medial geniculate body the temporal cortex seems to have only scanty connections with the thalamus, probably with the pulvinar (Bucy and Klüver, '40).

Since the cochlea projects to both temporal lobes, deafness can be produced from a cortical lesion only if the both supratemporal planes are destroyed; such lesions are rare (Mott and Barrett, '07). In man it is generally stated that the right temporal lobe is a silent area; this statement is undoubtedly due to extensive intercortical connections of the temporal lobes which make it necessary to destroy them both in order to get a clear picture of their importance. No such human cases are recorded but, in the monkey, most extraordinary results follow (Klüver and Bucy, '37) the bilateral removal of TA, TE, and TG. The animal no longer shows fear or anger; it approaches any object but seems not to recognize its nature on the basis of visual perception alone but examines it by taste and smell; there are also very marked changes in sexual behavior and dietary habits. In man lesions of the left temporal lobe cause aphasia of Wernicke's type, as is well known (Nielsen, '46). We know nothing of the functions of the basal regions of the temporal lobes (TF, TH).

All of the posterior part of the cerebral hemisphere is organized, therefore, in similar fashion around the influx of three sensory systems—visual, auditory, and somesthetic. In each instance the area in which the sensory impulses arrive tends to become increasingly granular—koniocortex. Around each koniocortex is a zone which contains large pyramidal cells in the deeper part of the third layer followed by a vast intermediate area of generalized cortex so nearly identical in all its parts as to make subdivision very precarious. Most of

the temporal lobe, which, it should be remembered, is a vast ventral outpocketing from the intermediate region between the parietal and occipital lobes, is covered by this generalized cortex. Whenever a koniocortex is injured we are blind, deaf, or cannot feel to a greater or lesser extent depending upon the extent and location of the injury. When the parakoniocortex is injured we may see or feel or hear but cannot recognize what it is that we sense. Injuries to the perisensory cortex produce more complicated disturbances of functions depending on the correlation of sensory data, such as alexia, jargonaphasia, apraxia, or somatotopagnosia.

We must mention another prominent sense which we have not yet discussed, the sense of taste. We have no evidence that gustatory impulses reach the cerebral cortex but there is some evidence that there may be a gustatory receptive area on the parietal operculum (Ruch and Patton, '46).

We should mention also the second receptive areas for touch, vision, and hearing which have recently been discovered (Woolsey, '47). We may expect such modern electrical methods of investigation to increase our knowledge of the sensory regions of the cortex with great rapidity.

Between the temporal and fronto-parietal opercula one finds a small area of buried cortex known as the Island of Reil. Next to nothing is known of its functions or connections and it may be dismissed from further consideration. It seems to get covered over because it lies lateral to the basal ganglia and cannot be evaginated by increase in size of the lateral ventricles. The temporal lobe seems to be pulled down out of the basal parieto-occipital region during development by the powerful connection of this region with the orbital surface of the frontal lobe through the uncinate tract; the expansion of the temporal and fronto-parietal regions then must bulge above and below the island to form the deep Sylvian fissure.

The cortex anterior to the central sulcus may be divided into three fundamental areas which differ sufficiently in structure to indicate some important difference in function, (1) the anterior limbic area, (2) the precentral motor area, and (3) the frontal area proper. The first of these will be discussed

later in connection with the rest of the medial surface of the hemisphere.

The precentral motor cortex (FA + FB) is well-known and we need to spend little time with it. It is characterized, in the adult, by absence of the granular layers. It extends from just above the callosomarginal sulcus on the medial surface of the hemisphere in a broad band onto the lateral surface anterior to the central sulcus and covering its anterior wall. Broader above, it may recede inferiorly into the anterior wall of the central sulcus. In its posterior part ($FA_\gamma$) are found the gigantic cells of the fifth layer known as Betz cells. It is known since the days of Fritz and Hitzig that electrical stimulation of the premotor cortex causes movements of muscles, so that it is often loosely referred to as the "electrically excitable" cortex. All of the cortex is, of course, electrically excitable and movements may be elicited by stimulation in regions behind the central sulcus so the term should be dropped. Moreover, even anterior to the central sulcus movements can be elicited from regions which are granular (FC); agranularity and excitability are not synonymous but certainly this characteristic of the cortex seems to facilitate excitability, the most exquisitely localized movements being elicitable from the posterior part of the agranular premotor cortex. As one moves forward from the central sulcus the movements elicited by stimulation become grosser and more difficult. Different parts of the skeletal musculature are represented in this cortex in a definite order (Penfield and Erickson, '41).

Destructive lesions of the agranular precentral cortex cause voluntary paralyses of the musculature of the opposite half of the body in a definite orderly sequence (Athanasiu-Benisti, '18).

The agranular precentral cortex (FA + FB) receives afferent proprioceptive impulses (Poliak, '32) either via the medial lemniscus or the brachium conjunctivum and the lateral nuclear mass of the thalamus (Walker, '38). It receives a heavy influx also from the cortex of the postcentral gyrus, the infraparietal plane (French, Sugar, Chusid) and less from various other parietal regions, and sends correlation fibers back to the same regions, especially to the superior

parietal lobule. From the agranular precentral cortex there is also, of course, a heavy projection to the subthalamic nucleus, substantia nigra, red nucleus, pontine nuclei, nuclei of the bulbar nerves and to the spinal cord. A vast amount of investigation of this region of the cortex has been summarized in the monograph on the precentral motor cortex edited by Bucy ('44).

The anterior part of the frontal lobe is covered by a generalized cortex (FD) very similar to that over the inferior parietal lobule or second temporal convolution. The transition from the agranular motor cortex (FB) to the eulaminate frontal cortex (FD) is very gradual; this intermediate dysgranular zone is known as FC; by definition it contains a very poor internal granular layer and its boundaries are very vague. Electrical stimulation in its neighborhood gives, after long delay, movements of the eyes and pupils which persist after the stimulus is removed. This zone is spoken of by physiologists as the "eye field" of the frontal lobe, since movements of the eyes can be elicited by stimulation of other parts of the cortex. As one follows this zone down toward the frontal operculum one can elicit not only movements of the eyes but also other effects such as complicated licking, chewing, or swallowing movements or arrest of respiration. The lower part of FC varies somewhat in structure and is known as FCBm. It is in this region that Broca's area is situated. Electrical stimulation in this region causes movements of the vocal cords. Lesions here of the left hemisphere of right-handed persons cause motor aphasia.

Anterior to the zone FC the cortex becomes well laminated with definite internal and external granular layers. It becomes thinner and its cells smaller toward the pole (FDE) but otherwise varies little. Vague subareas are distinguished in which the cells are larger (FDΓ) or smaller (FDp) or more uniform (FDΔ) or heaped up in the fifth layer (FDL) but the significance of these tenuous variations is unknown. The whole region has relations with the large dorsomedial nucleus of the thalamus (Freeman, '47) and develops *pari passu* with it. Intercortical relations are extensive with the inferior parietal lobule (PG) and the first and second temporal

convolutions (TA + $TE_1$) and with the parietal region on the medial surface ($LC_1$).

Lesions of the frontal region proper result in serious alterations of behavior making social adjustment difficult (Brickner, '36). When its thalamic relations are severed by the operation known as lobotomy one of the favorable results is the alleviation of anxiety (Freeman and Watts, '42).

It remains to mention briefly the limbic lobe. Lying on the medial surface above the corpus callosum the cingulate gyrus has an anterior region (LA) which is agranular and a posterior region ($LC_2$) which is eulaminate. The structure of the posterior limbic area resembles isocortex but that of the anterior limbic area varies considerably from that of the remaining agranular cortex and is sometimes called mesocortex. Around the splenium of the corpus callosum is a koniocortex (LE) which must receive olfactory impulses. The posterior limbic area receives also fibers from the mamillary bodies (Woolsey, Dick, Franz) and projects to the anterior nucleus of the thalamus (Bonin and Bailey, '47). Stimulation of the anterior limbic area causes alterations of respiration, of blood pressure, piloerection, contraction of the bladder and suppression of muscular contraction (Smith, '07). Lesions of this area in the macaque monkey cause decreased activity, indifference, excessive vocalization and piloerection (Smith). On the basis of the little we know of the limbic lobe it is supposed to play a role in experiencing emotion and in emotional expression (Papez, '37).

We have completed our rapid survey of the cerebral cortex, noting only those facts which seem to us at the present time to have functional significance. Using all the sorts of related information at our disposal we have tried to understand in how far the various regions of the cerebral cortex have developed specialized function and how these developments are reflected in the connections and internal structure of the cortex. We have now to come back to another fact which tends to be forgotten—that vast areas of the cerebral cortex have a structure so similar as to be differentiated only with the greatest difficulty. Surely this similarity must reflect some general function common to the entire isocortex. In order to

determine what this might be we must delve deeper into the intrinsic structure of the cortex. It is clear that the cerebral cortex is a vast controlling mechanism superimposed on the simpler fixed neural circuits of the neuraxis, but just how the cortex performs this function is not so clear.

With the methods we have hitherto used one can see that its cells form six horizontal layers and also that they tend to be arranged in columns perpendicular to the layers. In order to follow the ramifications of the processes of these cells it is necessary to use the Golgi method which has the peculiarity of impregnating isolated entire neurones. The details of this internal structure of the cortex have been most clearly stated by Lorente de Nó ('43). Their functional implications are only beginning to be vaguely suspected (Halstead, '47; McCulloch, '47). It is evident that most of the cerebral cortex (the vast areas of practically identical structure) consists of neuronal chains and circuits in a state of active equilibrium which is constantly shifting as betrayed by the electrical fluctuations of voltage within it (Berger). It is not constructed on the pattern of a telephone exchange to give an identical response to an identical stimulus but is rather a fluctuating pool whose response will depend on its state of equilibrium at the moment an impulse enters it. It is this plasticity which makes choice and learning possible.

The neurologist wants to understand the organization of the cerebral cortex for two reasons, as a matter of intellectual curiosity and also in order to devise means of correcting its disorders. Before a medical audience I need to give no illustrations of the manner in which knowledge of the regional specialization of function is used to localize a diseased process in the brain. One infers from the altered function where the trouble lies. When, in 1884, Bennett localized a tumor of the precentral motor cortex by inference from the symptoms alone, and persuaded the surgeon Godlee to remove it, the feat became justly celebrated and started an epoch in the practical application of neurological knowledge. When Berger convinced the world, in 1929, that the cortex was the site of electrical fluctuations which could be registered through the

intact skull and scalp he opened another epoch. Electroencephalography is proving of ever greater usefulness in the localization of lesions in the brain. A third great epoch began when Egas Moniz ('35) induced the surgeon Almeida Lima to detach the frontal lobes of an alienated patient from its thalamic connections—a procedure he called leucotomy.

Whether the surgeon intervenes on the brain in order to remove a tumor, to suppress an epileptic attack or to remove anxiety, he needs as detailed a knowledge as possible of the structure and function of the brain. Alas! his troubles do not cease when he has exposed the brain at operation. The surface configuration of the human cortex is so variable as to give uncertain aid to the localization of even our present vaguely distinguished areas. Electrical stimulation can locate the precentral motor cortex and guide the treatment of motor abnormalities such as athetosis and tremor (Bucy, '44) but is useless over vast areas of the cortex. So far as we are aware there has been no attempt to apply to man the method of Marshall, Woolsey, and Bard for the location of the sensory projections.

Within the brain one is even more at sea. In the soft white matter the identification of a desired tract is practically impossible. Clarke ('20) devised a stereotaxic instrument for use on the cat and monkey which enabled him to destroy any desired structure at will; so far this instrument has not been successfully adapted for use on man. Defective as our knowledge is of the regional physiology of the brain it has outstripped our practical utilization of it.

Satisfactory solution of the practical problems, I am sure, will initiate a great improvement in our ability to treat disorders of the brain successfully. For example, the operation of Moniz is very crude, detaching as it does almost the entire frontal lobes from the rest of the brain. While it calms anxiety it creates other difficulties for the patient who remains afterward with lessened drive and selfcontrol. If we only knew what fibers were essential and how to identify them we could perhaps remove the patient's anxiety and leave him his control. If we remember how many things once thought im-

possible are commonplace today we will never believe such results to be impossible. They are the goals of all our endeavor.

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# THE CHANGING CHALLENGE TO PUBLIC HEALTH

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What time holds in store for the world is difficult to predict. The future is like a stage on which the props are all set and the lines rehearsed, but which is still hidden from the waiting audience. Who could have foreseen the shattering events which followed both before and after the Battle of Britain, in which the course of history was turned as certainly as it had been twelve hundred years before at the Battle of Tours, where it was decided whether Europe was to be Christian or Moslem? All that can be safely said is that the world has been shaken violently by a revolution in its politics, economics, communications, and weapons, which is forcing us to revise all of the historic conceptions to which we have done homage for so many years. The only certainty is that the present pattern of the world belongs to an outmoded design which is on its way out of history. With the inevitable reorganization of society, the opinions and conclusions as to the scope of the public health field are undergoing changes. There are as many perspectives as there are interests concerned, and one's opinion is almost always influenced by one's own particular interest and background.

A glance into the crystal ball, and the magic word "freedom" flickers into sight. A few lines may not be amiss about this word, so beloved by politicians and propagandists alike. Freedom without qualifications is an abstract noun, whose meaning varies with each person's sense of value. In sober moments of meditation, everyone of us must surely realize that no one can be fully free. Some men and women prefer freedom from financial cares, others the freedom to pursue all branches of medical practice and art for the benefit of society and they therefore chain themselves to the Health Department and the so-called "bogey" of bureaucracy. Strange, that those who are

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often most voluble in crying aloud that they will never, never be slaves, usually endure without a murmur the slavery of a routine occupation. There is, however, one freedom that all of us desire: *that is, freedom from ill health for everybody.* Man has always considered health as an inalienable right, while he resented disease as a misfortune. He does not appreciate the fact that health is a privilege which requires continuous efforts in order to be maintained.

The treatment of sick persons and their restoration to health, the declared main objective of medicine, the dental and the nursing professions, has been practiced without an attempt to clarify the very meaning of the words "disease" and "health." Until quite recently, the public health services, dealing with urgent and sometimes catastrophic problems, were more concerned with the prevention and control of infectious diseases in the community than with the building of healthy communities. The cure or alleviation of disease is still regarded as the sole and proper function of a disciple of the art and science of medicine. Health teaching is merely practiced as a side line.

Let us frankly admit that our thinking about health has been definitely confused. For example, one hears the curious term "positive health" as though there were some other sort of health that was "negative." Health in its dynamics resembles disease, and like disease is a continuing and fluctuant process rather than a static one; its features vary with age, sex, and other circumstances. Between health and disease, be it admitted, there is no sharp and clear-cut boundary. Certainly, health is something quite different from the state of "no demonstrable disease" with which it has been too readily confused.

Young Army recruits who were enrolled by the thousands under category 1-A rapidly gained in weight and improved in appetite, bearing and efficiency under the influence of good food, fresh air, and physical training; does this not suggest that, although "no disease" was found, "A-1" and healthy are not identical, and that the conditions requisite for health were lacking in the previous civilian life and work of a large proportion of servicemen and women. Improved school meals

and other refinements of healthful living have helped to produce significant improvements in the physical, mental, and moral growth and stature of elementary school children, and have brought them nearer to a state of health than was possible for the children of earlier generations. The changes in state of mind and body of one who finally takes a long-overdue holiday furnishes by striking contrast an indication of the breach between a condition of "no demonstrable disease" and a condition of health.

It is clear that health is something worthy of study for its own sake, and for the better application of knowledge to its promotion and maintenance. Like disease, there is about it a great deal which remains to be discovered: its causes, its manifestations and its consequences. Methods of observation and experimentation already employed in the clinic could be readily adapted to these purposes. Unfortunately, too many of our "normal standards" employed in the ward and the laboratory have been based upon the examination of patients in varying states of health. In consequence, a worldwide acceptance of uncontrolled tests and methods has no doubt created countless invalids through the indiscriminate use of findings which often represented no more than the range of "normal" variability.

Many studies of a very fundamental nature will be necessary for the orderly development of programs and policies in education for health. The symptoms and signs of health and their variation with age and sex are available for study in the home, at baby clinics and schools, and in our universities at the student health services, spanning the more formative years of life which come between birth and full adulthood. It is already known that sound parentage, proper standards of nutrition and housing, adequate sleep, and holidays are prominent among the causes of health. Some of the consequences of health, like those of disease, are measurable in terms of output or by other forms of achievement, and can be recorded both qualitatively and quantitatively in the individual by careful observation, and physical and psychological assessments. The social or nonmedical factors affecting a people's health opportunity which still remain to be assessed

are numerous. Sound health policy must in the future include improvements in the social and economic structure. Lack of proper values and ignorance, however, remain the most potent causes of loss of health. Much of the present day unfitness is due to continuing *ignorance of well established facts or neglect of the indisputable rules of living.*

*One of the most astonishing lessons learned from the Selective Service medical examinations was the proportion of the public that is willing to endure or fails to recognize, reveal, or correct menacing minor defects.* In referring to this, Colonel Leonard G. Rountree, Chief of the Medical Division of the Selective Service System, has said: "This cannot be ascribed wholly to ignorance on the public's part. Instruction in these matters has not been lacking. Teaching pertaining to health, physical fitness and the need of periodic examinations has been emphasized everywhere and at all times, in and out of season. Medical and dental clinics abound, especially in the urban centers where these defects are most commonly encountered. Why, then, are these defects, deficiencies, disorders, and diseases so rampant? *Obviously, our people have false standards of values.* No other explanation seems possible, for many registrants who were living museums of minor defects were at the same time well dressed, lived in good homes, owned fine radios and not infrequently expensive cars. Evidently, the desire for luxury and comfort with many people takes precedence over their willingness to seek good health and physical fitness. The Selective Service System also uncovered data indicating that low standards of living commonly prevail in this land of plenty."

In the future, this lack of proper values must be met by *public health education. True education,* not merely the distribution of facts. In approaching this very large problem, the question to be asked is: Whom should we educate and how shall we educate them? Certainly, the answer to the first question is, "Everyone." Health, not only as a right of citizenship but as a duty, can be made a suitable and arresting subject for lectures and discussion groups. The role of diet and cooking, cleanliness and the use of leisure should have special emphasis. The periodic health examination must in

time become accepted practice not only in infancy and childhood and for the person leaving high school, but it also must be made a statutory preliminary to student life, employment, and at intervals thereafter. The leaders of industry have still to learn that their most sensitive and indispensable machine is the human machine, and that the improvement of working conditions is both a human duty and urgent economic necessity. The doctors and statisticians and welfare officers must be their teachers, the engineers and architects their associates.

But how are we to devise an education for the legislator? Would it be too much to suggest that simple courses of instruction in vital statistics; in the correlation of mortality with occupation and overcrowding; in the recreational, nutritional and environmental needs of the people should be made available to those who later sit in city and county councils or on the boards of supervisors? The health officer speaking before these groups often tends to lay too much stress on the achievements and too little on what has yet to be done. Where are the statesmen who with Benjamin Disraeli would say: "The health of the people is really the foundation upon which all their happiness and all their power of state depend."

In this connection, thoughts recently expressed by Dr. Alan Gregg are eminently appropriate. He says: "The wisest course for us as doctors is to inform and instruct the public, constantly and competently, for the education of the public is the one inexhaustible source of strength in promoting the public health. Is there any sense in doing so little as we are doing now to inform those in authority as to what they could have?—the art of the politician is described as the ability to convert private desires into public demand. It seems to me that the plain duty of a doctor as soon as he knows with absolute certainty what causes a disease is to convert private scientific knowledge into public information and to be ready to act on a public demand for action."

These wise recommendations emphasize again that advances in Public Health can only be made provided the causes of health and disease are understood. The concept of the specific contagious nature of diseases inspired the magnificent advances of the past; the dramatic reduction of illness and

death due to infectious disease attests to the value of such a concept. But today the doctrine holding that there is a single or specific cause for each disease entity is untenable. A purely bacteriological explanation pays little heed to the complex factors which influence the host-parasite relationship in a disease like rheumatic fever. The more quickly it is realized that causation is a constellation of predisposing, provoking and perpetuating factors, the more rapidly will progress be made. Nevertheless, the rather naive attempts to reduce everything to the simplest terms continue to focus attention upon provoking factors. If it is not a microbe it must be the fearful unknown, a virus, or more recently, a nutritional defect. There are many disturbances in which neither infection nor nutrition plays a role. Such affective elements as hereditary characteristics, accumulated fatigue, exposure, or psychic and somatic injuries, all predisposing or perpetuating factors, have only recently received attention under the impact of the experiences collected in the induction centers and on the battlefield.

Dr. Gregg's admonition "to be ready to act on a public demand for action" deserves a considerable amount of thought. Until the adequacy of the measures and tools required to furnish the service is known, and the competency of the personnel entrusted with a given preventive step has been thoroughly tested, it is doubtless premature to embark on certain programs which promote health. Until the Health Departments, the medical schools, the physicians and nurses can meet any demand for service in a particular health field with adequate facilities and technics, the risk of losing the confidence of the public constantly threatens. Experiences in New York have shown that as a result of a campaign by the American Cancer Society there has developed a great consumers' demand for doing something about cancer; a large segment of the population has been made cancer conscious, and the facilities to satisfy their demands are lacking. It is frequently not appreciated that the mass application of routinized diagnostic and therapeutic procedures so effective in the realm of the acute communicable diseases of childhood is worthless in the prevention of the degenerative disorders of later years.

There is much practical good that can be accomplished through concentrated study of the individual patient and the better application of existing knowledge to his case. To detect insidious new growth or other physiologic disorders in their incipiency, when they are amenable to control, requires highly specialized knowledge and skill and elaborate facilities.

Ultimately, of course, the patients must be guided by personalized, individual education. In large cities opportunities to explore such progressive, individualized programs are available; but not in the open spaces of the West. In the rural sections of the West the resources for health are often in a primitive state of development. Many an idealistic young physician, who decided to go into public health work after reasoning out for himself that preventive medicine brought the greatest good to the largest number with the least expense, doubtless has experienced keen disappointments. Although he may be successful according to public health standards, he cannot be satisfied in forever telling his people about the services which medicine provides, only to have them disillusioned when these services are not available. He does not blame his teachers for his lack, as even they probably were not certain that the gospel could be practiced in the way in which they were preaching it. So faced with the specter of defeat, the majority of the once-eager band drift back to the cities, but on rare occasions an individual fired by social consciousness refuses to admit defeat. He begins. He creates the services which maternal and infant emergency demand by setting up small clinics or hospitals with laboratory facilities. Next, he addresses himself to school work, and the neglected protection of the people of his community against the prevailing occupational hazards. He believes in diagnosis first, and then treatment; and he is honest with himself in referring all patients that he is not competent to diagnose or treat. He does not do any surgery because he does not consider himself adequately trained. Notwithstanding all this, the confidence of the public in him is complete because his health promotion program is commensurate with the facilities and technics at his disposal. In his rare hours of quiet meditation he ponders over the problem of chronic disease which

saps the strength of his community economically as well as medically. Although far from satisfied, he realizes that the people in his community are better off than the 15 million who live in the 1,200 counties that have no hospitals at all, for to them the essential facilities and personnel required to promote health are inaccessible. A glance through the professional literature which passes over his crowded desk focuses his attention on some of the unanswered questions challenging medical science today. There is the increasing importance of mental illness.

In the quarter century from 1912 to 1936, the rate for first admissions to State Mental Hospitals per 100,000 population over 40 years of age increased from 7.7 to 49. This is a rise of more than 600 per cent. The importance of organic disease of the nervous system may be further illustrated by the fact that of all new admissions (110,323 cases) to mental hospitals in the United States in 1938, 49 per cent were associated with structural diseases of the central nervous system. More than one-third of all permanent occupants of such institutions suffer from organic diseases of the central nervous system. Thus, roughly one-half of all new admissions and one-third of all permanent inmates of State Hospitals suffer from organic diseases of the central nervous system.

Stanley Cobb (*Borderlands of Psychiatry*, pp. 166; Cambridge: Harvard University Press, 1943) estimates that, in addition to the thousands of mental hospital inmates, there are in the United States 650,000 patients with epilepsy and 600,000 with other neurological diseases. To this already large group have to be added the victims of injuries to the brain. Thirty-five thousand persons were killed in 1940 in traffic accidents in the United States, and 1,320,000 were injured. A large proportion of these cases can be presumed to have suffered from head injuries, the care of which belongs in the domain of neurologists and neurosurgeons. A recent report of the Metropolitan Life Insurance Company states that brain tumors now account for more than 1 per cent of deaths.

The above figures indicate that *organic diseases of the central nervous system* occupy second place among the disabling mental afflictions, leaving the first place to mental diseases

such as Schizophrenia; or, expressed in other words, one can say *that between 1 to 2 per cent of the normal population suffers from nervous disease.* The importance to be attached to the proper care of these patients, and to the teaching and development of knowledge in this field is obvious. Recent reports from New York, for example, emphasize the need for psychiatric rehabilitation; of 135,500 New York men requiring such aid, only about 5,400 are receiving it. These figures indicate the great gap between need and available services, but also something of the barrier of public mistrust in regard to psychiatric aid that remains to be broken down if a healthy society is to be achieved. Clearly, these findings and reflections on mental health have far-reaching implications for the nation as a whole.

There is the problem of geriatrics. As more lives are saved from premature death, large numbers of the population will survive to ripe old age. This phenomenon naturally will continue to operate as long as public health practices reach higher levels. The majority of individuals surviving into the age period above 65 enjoy far from the optimum of health. Many persons survive to ages in which there occurs a sharp rise in the incidence of vascular disease, diabetes, gout, cancer, etc. The menace of the chronic, progressive diseases associated with senescence is greatest in the two decades from 40 to 60. Public health must take the viewpoint that more may be accomplished for the aging than for the aged, and it must emphasize the adoption of *preventive measures* during these critical years 40 to 60 wherein the aging begins. The multitude of present and impending problems in sociologic, economic, political, religious, and educational fields incident to the approximately 9 million persons of age 65 or more in the United States is evident to everybody. The clamor of the aged for economic security may be heard throughout the land. And the mounting economic and social burden of chronic and disabling mental and physical disease is appalling. *Medical science must search*, discover and find means for controlling or retarding its progression.

Public health in using all scientific knowledge owes a great deal to experimental medical research. The development of

the sciences of physiology, bacteriology, and biochemistry, the chief contributing sciences to public health, depends on research requiring animal experiments. Many of the most striking advances in public health merely reflect the knowledge accrued in laboratories and clinics as applied administratively. The immunological control of communicable diseases rests on planned experiments on animals. Quantitative studies and refinement in assessment of the immunity response are constantly used to determine the potency of a protective agent before it is placed in the hands of the health officer. The discovery of vitamins and the recognition of their influence upon the health of man and animals was based on prolonged animal experiments. But concurrently with this laboratory work, public health field studies demonstrated that many people were not receiving the minimum daily intake of essential food, and that nutritional deficiencies manifest themselves in such pathological conditions as rickets and the simple goiter. The experimental reproduction of a disease state led to the discovery of insulin in the treatment of diabetes, of liver extract and more recently revealed the influence of folic acid on blood formation. The application of physiology to industry has improved industrial well-being. Knowledge gained in the research laboratories has made the lives of millions of people healthier and longer. Medical research has indeed had profound influence upon the course of history and the national health.

It is time that those responsible for the nation's health should recognize the need for devoting effort and resources commensurate with the magnitude and importance of the problems to be solved. Needless to say, such a program will require a revision in the concept of medical research and the allocation of more funds than the relatively small sums spent before the War. Up to the present, medical research has been conducted primarily in medical schools, hospitals, and universities, largely on the plane of an amateur enterprise. With few exceptions, it has been and still is a part-time and spare-time work of enthusiastic individuals whose jobs are not research. In the clinical sciences, progress depends largely

on the spare-time efforts of medical students, internes, practicing physicians, and teachers. In the entire country there is only a handful of full-time clinical research workers attached as fellows to the staffs of a small number of university hospitals or medical schools. These workers are principally transients for whom a year or two of full-time research is a stepping stone for a teaching position or practice. It is not heartening to know that in the basic medical sciences, biological and organic chemistry, pathology and pharmacology, research is also largely a part-time endeavor; the workers are primarily medical school teachers and secondarily researchers. They are burdened with heavy teaching schedules, routine examinations of specimens from the clinics, administrative, and committee work. They have more uninterrupted time for research than most, however, since they are relieved at least of caring for patients. At best, it is still spare-time research.

Considering the handicaps under which these investigators labor, the research performances of the past and present have been epoch making, and the contributions to human welfare have indeed been remarkable. But medical research is too important to human welfare to be relegated to the position of a spare-time endeavor of busy physicians and teachers. The task is big enough and important enough to command the full-time devotion of thousands of highly skilled, carefully selected investigators whose responsibility and obligation is one thing—research. There should be attached to each medical school, hospital, and laboratory a corps of full-time research workers equal in number, rank and standing to the teachers, physicians, and assistants. Instead of one National Institute of Health, one or two cancer institutes and about a dozen other institutions devoted wholly to medical research, there should be a hundred or more such establishments. To attract competent workers to full-time research there must also be adequate compensation; for the glory of contributing to human welfare and progress is not enough. Medical schools and universities have become alarmed at the exodus of their best brains to medical practice or to industry. Appeals to refrain from depleting the stock of research workers are futile until

the institutions are in a position to pay their members a living wage.

This unpleasant recital of facts raises the question: Is Society willing to pay for better health and longer life? Until the advent of the atomic bomb few appreciated that even in science it takes money to produce results. It was then suddenly realized that brains with adequate financial support can produce the most destructive weapon. Equally spectacular results in saving lives can be achieved with American brains provided we are less pennywise in our spending. Until quite recently, the public has been largely unaware of how little was actually being spent for medical research. It has been estimated that in 1944 the paltry sum of $615,000 was devoted to research in the diseases of the heart and the blood vessels, which killed more than one-half million, and were responsible for the disability of some eight and one-half million persons in the United States. Yet in the same year more than $31,000,000 was spent for cigarette advertising. During the War the Office of Scientific Research and Development devoted $15,000,000 to medical research, but American business spent more than a billion dollars on war advertising. For tuberculosis research $865,000 must be contrasted with the $2,000,000 allocated for white pine blister rust control by agriculture.

As Goodpasture in an important address has recently pointed out, the financial support of research, heretofore largely dependent upon universities and philanthropic foundations, is no longer adequate. Moreover, since industry has not devised a means for affording free financial aid to universities and hospitals, the only source of funds visible today is public or governmental support. This trend was visualized and amply documented in a valuable discussion on "American Medicine" published in 1937. Unanimous recognition is there given to the importance of government aid for the prevention of disease, the improvement of public health, elevation of the quality of medical care and the advancement of education (page 1291). It was feared that support from this source might encounter difficulties in the selection of projects, and be subject to political interests. This fear has been alleviated by the interpretation which the Surgeon General of the United

States Public Health Service, Dr. Thomas Parran, Jr., has given to the Public Health Service Act of 1944 with respect to research and investigations.

Dr. C. J. Van Slyke, chief of the Research Grants Division, in his paper "New Horizons in Medical Research" makes the significant statement: "The program, based on United States Public Health Service Research Grants financed by public funds, supports research—conducted without governmental control—by independent scientists. The purpose of these grants is to stimulate research in medical and allied fields by making available funds for such research and by actively encouraging scientific investigation of specific problems on which scientists agree that urgently needed information is lacking. Accompanying this purpose is complete acceptance of a basic tenet of the philosophy upon which the scientific method rests: The integrity and independence of the research worker and his freedom from control, direction, regimentation, and outside interference."

Since the beginning of 1946, as a member of the National Advisory Health Council, it has been my privilege to be one of those who have welcomed and approved the principles and the programs of this financial aid, which so far has been allotted to basic fundamental research in 77 institutions, covering a total of 264 research projects in the amount of $3,900,000.

Before the Council has an opportunity to see the applications for grants, a group of consultant experts working as so-called Special Study Sections review the data submitted by the applicant, adjudge his qualifications and the nature of the project, and recommend appropriate action to the Council. Within the Study Section the status of research in the respective fields is analyzed. Neglected areas in which research is urgently needed receive special attention, and efforts are made to stimulate the interest of workers competent to explore the needed studies. This type of financial assistance has been further enhanced by Medical Research subsidies offered by the Navy and War Departments to universities. The latter group of organizations supporting research came into being at a time when lack of agreement among scientists as to the

best form and proper functions of a National Science Foundation prevented its establishment. This great expansion in Federal subsidy of Medical Research will doubtless exert a profound influence. How far it will influence the quality of younger scientists and their position in the over-all organization of full-time Medical Research will be watched with lively interest.

In a recent address before the American Philosophical Society, entitled "Trends in American Medical Research," Richard Harrison Shryock calls attention to several important facts. He points out that basic pure scientific research in cancer, for example, is now far better supported than is the search for cures. He justifies this approach, explaining it in the following way:

"At first glance this may seem a final reversal of the older American attitudes—a triumph of pure curiosity over utilitarianism. But so subtle are these distinctions today that one may interpret the phenomenon in just the opposite manner. It happens that the direct search for cancer cures is considered unlikely to yield results in the near future. Hence institutions are loath to support a man who goes on year after year in this direction with no results (Rous, Peyton: Concerning the Cancer Problem. *Amer. Scientist*, 34:335, July, 1946). After ten years, or twenty, he may only echo Godman's words of 1825: "The search for remedies led nowhere." No doubt it is unfortunate that the direct search for cures has so little support, for who knows—? But the fact remains that it is neglected here because its promise of utility is so uncertain. Conversely, basic research is relatively well maintained because of the hope that it may actually lead to prevention or cure sooner than will direct attacks on these problems. In a word, we still seek the useful in science; but no longer necessarily equate this—as did the American public a century ago—with work of an immediate and applied character.

Dr. Shryock continues: "The problems facing American medical science today are quite different from those which were pressing in 1900. After a century of colonial dependence, the United States finally emerged as an independent center of medical science. It need only be pointed out, in conclusion,

that nationalistic enthusiasm should not make the mistake of confusing independence with isolation. After 1918 the number of Americans who sought post-graduate training abroad rapidly declined. Many seemed to feel that native training facilities were now completely adequate, or even viewed any desire for foreign study whatever as a confession of cultural inferiority. This trend, with its implied threat of a 'continental complacency' (a view expressed by Dr. Alan Gregg of the Rockefeller Foundation), may actually be interpreted as a last vestige of colonialism—as an exaggerated assertion of independence rarely made in European societies. True scientific maturity implies rather the opportunity, now before this country, of exchanging students as well as knowledge freely with all other progressive lands."

A noteworthy feature of modern society is that its strength depends to an unprecedented degree upon the coöperation of its members. Since the specialist can live only through the help of others, coöperation is the corollary of specialization. Probably in no field of applied science is coöperation more essential than in public health.

Everybody knows that the congested life in a city requires careful attention to sanitation. Life in the world built by science is possible only with widespread coöperation. The first essential in securing coöperation is to develop a universal desire in the people to work together. Several methods of securing the will to coöperate have proved effective; one powerful method is to present the people with a common danger, such as the attacks by an enemy. In my judgment another, more powerful method is to present an inspiring objective. The report by the Committee on Local Health Units of the American Public Health Association published in March, 1945, succeeded in arousing a greater interest in coöperation among workers in the field and the movement has been gaining momentum since that time. One cannot read through the Proceedings of the recent conference at Ann Arbor without being impressed with a lasting appreciation that the most effective and economical method of providing public health service is through the local health unit. It was

clearly stated at that conference that the rights and prerogatives of the local units must be preserved at all costs. But one senses everywhere a feeling of uneasiness that the State Health Departments or a Federal agency, instead of seeking coöperation and functioning as advisory services, may ultimately become supervisory. Unfortunately, such trends are in some instances a definite reality. In fact, there is an unmistakable movement afoot seeking to pressure us into deserting the well proved pathways of coöperation, and which aims to shape the relationship between the state and local health agencies in the finest minutiae. Instead of serving as advisors and consultants to agencies established to render services on the local level, or to set standards in areas where local government cannot readily function, such state or federal agencies assume supervisory action. This trend is a part of a world-wide malady which permeates business, transportation and communications, and which is rationalized with the chant that centralized organization is necessary for "national survival" should we in the future collide with an authoritarian state.

Every social system is impelled toward insanities by its own rules. Cool reason tells us that health administration must be flexible and adaptable to changing conditions. When society follows a rigid model it is doomed to a totalitarian existence and ultimate death. Investigation and experiment by the trial and error method must be encouraged in every way possible. Just as in the research laboratory, where results are more likely to accrue from individual initiative blended with the coöperative group execution, so the local enthusiasm, interest, and energy of the component community will furnish results more certainly than will any regime of rigid standardization and bureaucratic supervision. In the address prepared by Goodpasture, to which I have already referred, the following paragraph expresses well the inherent dangers which the present trends and policies have for the progress of public health:

"The great threat of our age to human welfare, as I see it, is that Societies led or driven by industrialism are gathering the individual into their fold as a service unit. The individual

as a member of Society thus must do a Society's bidding, regardless of the particular pattern that social organization might temporarily represent. To the true scientist, the present frame of social organization is not the end of all wisdom but just another phenomenon to be viewed objectively in the course of his inquiries. The scientist's limits are the boundaries of the universe, and his function cannot, without destroying him, be limited to the service of any particular social order. Industrial, social, religious, and political patterns are not yet drawn to serve mankind. It is to be hoped that each governmental power will provide an oasis for students who are individual elements of mankind first and servants of Society last. Otherwise, intellectual growth will wither and die. Medicine is dedicated to the service of man and not to a social order. In this relation, Medical Research in its broadest sense has a preeminent call upon every social structure for support not merely for immediate needs but for the discovery of broad principles upon which the health of mankind depends. Let each social order therefore give the scientist a free hand and provide him with the environment and the tools he needs; make him accessible to students, for he is essentially a teacher; make the university his home; and *otherwise, for humanity's sake, leave him alone.*"

Yes, and for humanity's sake protect the integrity and independence of the local health unit from control, regimentation, and rigid supervisory interference.

In the preceding discussion I have repeatedly mentioned the singular importance of the personnel required to furnish the public health services. The recruiting and training of health officers has been made the subject of discussion during the present meeting and therefore it is not necessary to enlarge on this subject; but it is timely to look at the position of some of the other workers. There is urgent need to promote greater understanding of the role of the 20,000 public health nurses who make 16,000,000 visits each year to one of every six families in the nation. Public health nursing services have grown until they now extend to all sections of the country, but there are still 1,133 counties, mainly in rural areas, which have no full-time public health nursing service. A primary

obstacle in the organization of such services is the lack of available trained personnel, for there is an immediate need for 8,000 more public health nurses. To reach the ratio of one nurse for each 2,000 of population as recommended by the United States Public Health Service, the present number of 20,000 will have to be tripled. The great need is, however, not confined to the public health nursing field. In the survey of nursing and nursing education published by the Commonwealth Fund as one of the studies of the New York Academy of Medicine's "Committee on Medicine and the Changing Order," it was pointed out that the scarcity of graduate nurses in common with most other medical services was felt most in the rural areas. This report and a more recent survey by the American Surgical Association indicated that in hospitals in urban areas the quantity of nursing was 55 to 60 per cent of that which was needed, and the quality of that supplied was down to 75 per cent. There is certainly a need to find a way to attract more qualified young women into the nursing profession. Suggestions to alleviate the shortage by the use of practical nurses have been bitterly criticized. Confusion in training and licensure of these workers, and lack of any definite plan to utilize the specialty nurse such as the public health nurse, the hospital nurse and the practical nurse, can only be solved through a coöperative study and action by all of the professional groups concerned.

A somewhat similar state of affairs exists with regard to the personnel required for the environmental control in sanitation. The awakened consciousness of sanitary conditions has stirred in the public new wishes and desires. The services of sanitation frequently demand no engineering methods, but a background in the biological and social sciences, since the majority of the tasks are inspectional, educational, and regulatory. At present most local budgets are to low to provide for well experienced engineers with a post-graduate education in public health. In the West, the well-trained sanitarian has taken the lead in filling these vacancies. He has proved his ability in many competitive examinations, and has justified the trust placed in him by the health administration. Notwithstanding, sincere but inadequately informed forces are

at work to dislodge him from his well earned position; they demand that six or seven years of formal education must be required to produce the type of worker who will be the guardian of sanitation. Time does not permit to elaborate, but recent observations on the development of more effective sanitation in food preserving plants by sanitarians have indicated again that they understood human behavior and how to suit it to their purposes much better than does the professional engineer.

How the services of the specialist such as the veterinarian, entomologist, mammalogist, and food technologist can be combined to best advantage with those of the public health engineer and sanitarian can only be decided after the economics of inspection, and the multitude of sanitary details in their relation to agriculture and business have been evaluated through a coöperative study and action on the part of all of the professional workers involved.

The synthesis of the factual data on all these problems will undoubtedly disclose that sanitary maintenance requires not additional legislative requirements, but a broad educational expansion. Many of the laws and regulations of today's public health codes are medieval and incompatible with newer scientific knowledge, and should be studied in such an inquiry. This critical analysis of needs in the field of public health should preferably be made by an unbiased association.

Before concluding this discussion, attention must be called to the new fields of activity which are coming under the administration of the State Department of Public Health. Dr. W. L. Halverson, of the California State Department of Health, kindly permitted me to see the preliminary report on a survey of hospital facilities in California. For the first time, standards are being developed on a governmental basis to regulate the safety, sanitation, and services of hospitals. Furthermore, to the California State Health Department has been delegated the responsibility for hospital planning on a statewide basis. Both of these are new fields of endeavor, foreign to the ordinary functions of sanitation and communicable disease control. The implications are tremendous. The

planning of a hospital program is a great responsibility, requiring a knowledge of socio-economic factors and their interplay. It calls for the training of competent personnel; the addition of hospital or medical administrators to the staff of the Health Department; and for the recruitment of more technical advisors who will be constantly at the disposal of the staff. This phase is off the planning board, and with the impetus it received from the Kellog Foundation it is well launched.

Closely interwoven with the problem of hospital service is naturally that of medical care. Perhaps public health is not yet willing to face realities. Yet, it is futile to attempt a separation of preventive and curative services, and to accept the dogma that medical care is not public health. Medical care through organized groups has lessened maternal mortality and halted the spread of disease. As always in periods of transition, the need for accepting responsibilities lags behind the advances in the field. There is considerable risk that if public health fails to appreciate the position and the significance of medical care in the promotion of health, some other governmental agency will be developed to administer the services. The implications are obvious—when this happens new relationships with all their troublesome ramifications must be developed. The future of health and medical care is still in a plastic, formative stage. It is in our hands. The coöperation stressed throughout this address cannot be secured without a free discussion of all the complex problems involved.

# THE VALUE AND ACCURACY OF THE VAGINAL SMEAR IN THE DIAGNOSIS OF UTERINE AND CERVICAL CANCER

JOHN KENNETH COX*

Many articles have emphasized the vaginal smear method of diagnosing uterine and cervical cancer since this method was introduced in 1941 by Papanicolaou and Traut. The number of deaths from all types of uterine cancer was 16,516 in 1941, and it had increased to 17,225 in 1945 in spite of the fact that a method of early detection of this type of cancer had been present for nearly four years. This fact is explained when we realize that few of the gynecologists and practically none of the general practitioners are as yet making use of this simple diagnostic method. Re-emphasis of the method and of its accuracy are therefore necessary and will be attempted in this article.

The procedure is based on the exfoliation of cancer cells into the vaginal secretions. These cancer cells have characteristics which make them appear different from cells normally found in the vaginal secretions. These characteristics are well described in an excellent monograph published in 1943 by Papanicolaou and Traut. Proof that these cells are really cancer cells is evidenced by the fact that at least 800 cases of uterine and cervical cancer have been diagnosed by this method. Further proof is the fact that biopsies on cases showing positive smears have shown an identical cytological picture as that seen in the vaginal smears on that same patient.

Taking the smears is quite simple. A small amount of the vaginal secretions is obtained by aspiration with a bulb-tipped glass pipette, and then the secretion is blown onto a clean labelled slide and spread thinly and evenly. The slide is then immersed immediately in a jar containing 50% ether-alcohol for fixing. The wet smears should be sent to a laboratory where they will be stained according to the technique described by Papanicolaou and Traut in their monograph.

*From the Baylor Hospital, Dallas, Texas. Received for publication, November 20, 1947.

The interpretation of the smears should be attempted by someone especially trained in the diagnosis of cancer by this method. The interpretation is not easy and only by studying many slides may one become efficient. The pathologists who have ignored or made light of the method because they do not have the advantage of seeing actual invasion of tissues, are now realizing that the method is becoming standard, and that they must do most of the interpretations of these smears. The value of technicians trained in the interpretation of these smears will be a subject for considerable argument, but technicians with an excellent cytological background may eventually provide us with the badly needed trained interpreters. However, interpretations made by casually trained individuals with limited experience are both worthless and dangerous.

In addition to the simple vaginal smear as described earlier in this paper, there have been several other attempts to increase the accuracy and range of the method. Ayre (1944) describes the cervical smear or endocervical smear as called by Papanicolaou (1943), and states that with this method there is a greater concentration of both fundal and cervical cancer cells, and thus they will be detected easier. His term "surface biopsy" seems appropriate. Endometrial smears can also be made as described by Papanicolaou (1943) by obtaining secretions through a metal cannula such as is used for insufflation of the tubes. Ayre (1945) describes a centrifuge technique in which the vaginal secretions are centrifuged, blocked, and sectioned just as if it were tissue. In the latest improvement, Ayre (1947) uses a wooden spatula to scrape the cells from the squamo-columnar junction of the cervix in order to obtain as many cells as possible from that area, because most carcinomas of the cervix are known to arise there.

A summary covering most of the literature has been made in order to determine the real accuracy of the vaginal smear method of diagnosing cancer. These are tabulated in Table I. From this it is seen that a total of approximately 800 cases of uterine cancer have been diagnosed by the vaginal smear, and its variations, with an average false positive error near 3% and an average false negative error closer to 5%.

TABLE I

*Summary of literature to ascertain the accuracy of the vaginal smear method for the diagnosis of cancer. The table shows the results of the various workers in this field, with their variations.*

| Author | Date | No. Pts. | No. Cancers | False Positives | % | False Negatives | % | Av. Deviation |
|---|---|---|---|---|---|---|---|---|
| Papanicolaou & Traut | Aug. 1943 | sev. thous. | 193+ | | | Ca of cervix | 1.3 | |
| Papanicolaou & Traut | Mar. 1945 | 3014 | 180 | | | Ca of cervix<br>Ca of endomet. | 3.2<br>9.3 | |
| Meigs & co-workers | Nov. 1943 | 220 | 62 | 4 | 2.6 | Ca of cervix<br>Ca of endomet. | 2.2<br>8.3 | |
| Meigs & co-workers | Jan. 1945 | 813 | | | 2.0 | | 7.1 | 2.8 |
| Meigs & co-workers | Oct. 1945 | 1015 | 154 | 25 | 2.9 | 16 | 10.3 | 4.0 |
| Meigs | Jan. 1947 | 2749 | 339 | Ca of cervix<br>Ca. of endomet. | 3.5<br>20.0 | | 6.1 | |
| Ayre | July 1944 | 75 | 40 | | | 2 | | |
| Ayre | June 1946 | 580 | 100 | 9 | 8 | 4 | 4 | |
| Ayre | Nov. 1946 | 2320 | 202+ | | | | | 2.96 |
| Jones Neustaedter MacKenzie | Feb. 1945 | 427 | 82+ | 9 | | 7 | | |
| McClure Cattell | June 1945 | 170 | 3 | 2 | | | | |
| Brown Kraushaar Bradbury | Apr. 1947 | 193 | 34 | | | | | |
| Total | | over 8800 | over 850 | | approx. 3 | approx. 5 | | |

At John Sealy Hospital, Galveston, during the past year and a half, an attempt has been made to determine the accuracy of this method of diagnosing uterine and cervical cancer. The results of this study are shown in Table II. The

TABLE II

*Cases diagnosed by vaginal smear method at John Sealy Hospital. Galveston, to determine the accuracy of this method.*

| Total No. Smears | Total No. Cases | No. Cancers | False Positives | % | False Negatives | % |
|---|---|---|---|---|---|---|
| 602 | 231 | 41 | 9–24 | 4.7–12.7 | 0–6 | 0–14.3 |

41 cancers included 5 adenocarcinomas of the corpus uteri, 2 adenocarcinomas of the cervix uteri, 33 squamous cell carcinomas of the cervix uteri, and 1 squamous cell carcinoma of the vulva. Figure 1 and Figure 2 are photomicrographs of cinoma cells of the corpus uteri found in the smears taken from a 77-year-old white woman.

It is impossible to evaluate the exact accuracy and for this reason Table III is given to show a clearer picture of the false positive and false negative groups. Group A of the false posi-

TABLE III

*This table is presented to more clearly show the false positive and false negative groups, with numbers of cases and percentages.*

| | | |
|---|---|---|
| False Positives—Total possible | 24 | or 12.7% |
| A. Negative biopsy but positive smear | 9 | or 4.7% |
| B. No biopsy but positive smear | 15 | |
| False Negatives—Total possible | 6 | or 14.3% |
| Probably cured cases | 3 | |
| Possibly cured cases | 2 | |
| Probably active cancer cases | 1 | or 2.4% |

smears taken from a 23-year-old Mexican woman with squamous cell carcinoma of the cervix. Figure 3 shows adenocartives included all patients with a positive vaginal smear who had had at least one biopsy. Group B were included as false positives because no biopsy has yet been obtained and because clinically these patients did not have cancer at the time of examination. None of these 15 patients have returned for follow-up studies.

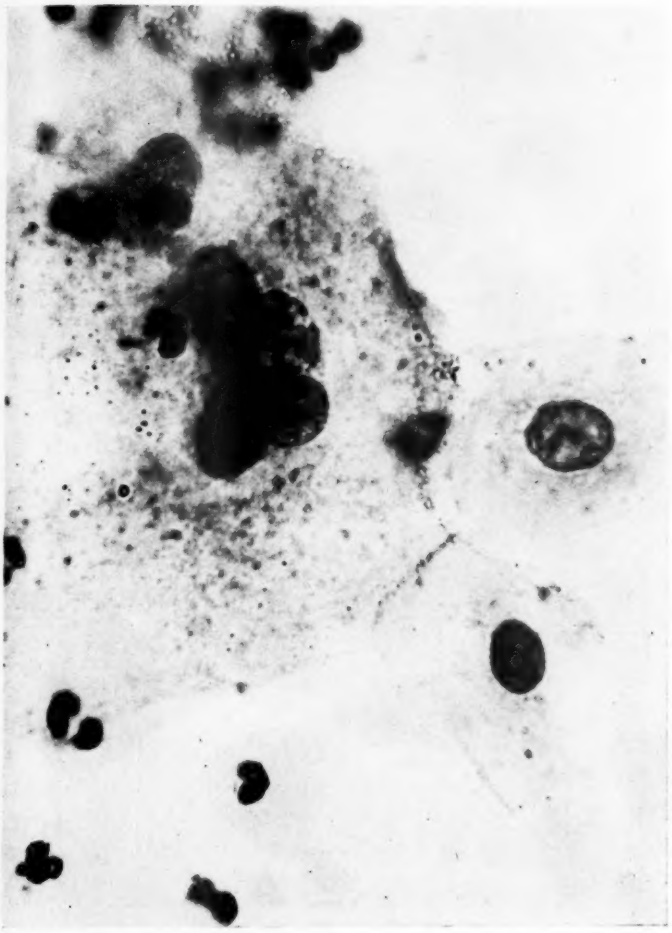

FIG. 1. Photomicrograph of vaginal smear taken from a 28-year-old Mexican female with squamous cell carcinoma of the cervix.

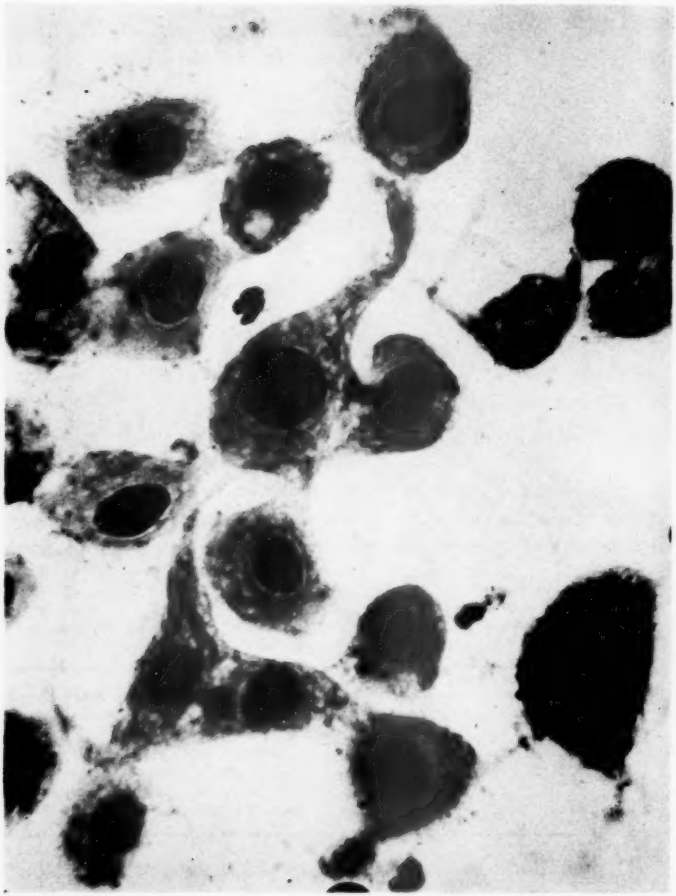

FIG. 2. Photomicrograph of vaginal smear taken from same patient as in figure 1.

FIG. 3. Photomicrograph of vaginal smear taken from a 77-year-old white woman with adenocarcinoma of the corpus uteri.

The 6 patients included as possible false negatives were all diagnosed as having carcinoma of the uterus or cervix by biopsy. All 6 had received some form of treatment before the smears were taken, and can be called "old cases." They included one patient who had been treated for an adenocarcinoma of the endometrium 33 years previously with a hysterectomy. Two other cases were diagnosed as early Stage I cancers of the cervix by biopsy and were treated by a Wertheim type of hysterectomy. The operative specimen of both cases revealed no carcinoma on repeated sections. A fourth case was a "3 year cure" of an adenocarcinoma of the endometrium which had been treated with a Wertheim type of operation and who had no evidence of recurrence at the time the smears were taken. A fifth case was that of a woman with squamous cell carcinoma of the cervix who had been treated with radium, and a year after initial treatment, showed negative biopsies. The sixth possible false negative was from a woman with a vesico-vaginal fistula, and urine smear revealed no cancer cells. These could be classed as 3 probable cures, 2 possible cures, and 1 probable false negative. This would bring the probable false negative to 2.4%.

The results of both other workers and of our own study show definitely that the vaginal smear is a good method of diagnosing cancer. The clinical use of the method will depend upon an evaluation of its accuracy and the importance of a false positive and a false negative report.

The significance of a negative smear report is that the patient probably does not have cancer of the uterus, but since still almost 5% of cancers of the uterus are not detected by the smear technique, it is not proof that the patient does not have one. Since there are some false negatives, the smear cannot replace the biopsy and the curettage.

The significance of a positive smear is similar to that of a positive Kline test for syphilis. It is in reality an exclusion type of test. Thus if a patient has a positive smear for cancer. a definite diagnosis should not be made, but rather an attempt to rule out a false positive should be done first. This means a biopsy. If the biopsy is then positive, the positive smear has been confirmed and the patient will be treated accordingly

with radiation or surgery. If the biopsy is negative, and another smear taken at the time of that biopsy, is again positive, the patient deserves another biopsy. After three negative biopsies and continued positive smears, it is felt that this patient should receive a cauterization or preferably a conization of the cervix. A positive smear for adenocarcinoma of the endometrium should be an indication for a curettage. Since the accuracy of diagnosing this type of cancer may yield as high as 20% false positives, one negative curettage should be sufficient to determine whether the report was correct or whether it fell into this group of false positives. It is important to remember, however, that negative vaginal smears and negative curetted material does not rule out adenocarcinoma of the endometrium. Even after as complete a curettage as possible, the clinician may have missed the lesion or the pathologist the tissue fragments showing cancer. Regardless of negative reports, it is wise to always treat a clinically positive case of endometrial cancer as cancer. A positive smear should help to make this decision.

This conservative type of management of interpreting what to do with patients with positive vaginal smears for cancer can be criticized because not all cancers are picked up by biopsy or curettage, but it is because of the large number of false positives that this management was selected, in place of hysterectomy. In our series for the 35 patients diagnosed correctly by the smear as having cancer, up to 24 patients were included as possible false positives. This means that only 2 out of 3 might actually have cancer. This ratio would probably be much lower if taken from a routine survey of patients with no cancer symptoms. Thus many patients would be unnecessarily subjected to surgery or radiation and to the mental handicap that goes with the diagnosis of cancer.

## Summary

The vaginal smear method of diagnosing cancer of the uterus and cervix is recommended and outlined. The accuracy of the method is evaluated by tabulation of the results of various workers. The results of a study of vaginal smears made on 231 patients at John Sealy Hospital in Galveston, Texas, are

presented. An evaluation of the significance of false positive and false negative reports is presented. Conservative management is recommended for patients with positive smears unless the smears can be confirmed by biopsy.

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# INHIBITION OF TYPHUS AND SPOTTED FEVER IN GUINEA PIGS BY INTRADERMAL INOCULATION OF ANTIORGAN SERA AND OF CERTAIN NORMAL SERA*

LUDWIK ANIGSTEIN, DOROTHY M. WHITNEY, AND JOE BENINSON

The mechanism of action of antireticular cytotoxic serum (ACS of Bogomolets, 1943, REIS of Pomerat and Anigstein, 1945) on animal tissues *in vivo* and *in vitro* still requires elucidation. While the damaging effect of massive doses of the antisera on animal organs (Anigstein and Pomerat, 1945) can find a plausible explanation in terms of classic immunology, a stimulating action of minute doses would be more difficult to explain. In the broader immunological sense, ACS (REIS) is embodied in the designation Antiorgan Serum which contains multiform antibodies, induced by the mosaic of cellular and chemical structures of the organ as antigen. The possible role of the antiorgan serum in the defenses of the host against infections recently revived the interest of investigators and is the subject of the present study.

The historical background of the antiorgan serum covers the period of the past 50 years beginning with Metchnikoff (1900), who by inoculating guinea pigs with rabbit testicular tissue produced a serum which proved spermotoxic to rabbits. Using spermotoxin as antigen Metchnikoff then prepared an antispermotoxic serum. Consequently, not only a cytotoxic serum but also an anticytotoxic serum was originated almost half a century ago. These developments were followed by extensive studies on the serological properties of various animal tissues, organs and their juices leading to the establishment of species and organ specificity (see Landsteiner, 1945). The discovery by Forssman (1911) of the heterophile antibodies added to the diversity of problems pertaining to antiorgan sera.

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A new version of Metchnikoff's ideas on cellular defense mechanisms was offered by Bogomolets with emphasis placed on the connective tissue and the RES. Recognizing the damaging effect of cytotoxic sera and Metchnikoff's suggestion that small doses of toxic substances may stimulate, Bogomolets (1943) believed that the whole connective tissue system could be stimulated by minute doses of antiorgan serum.

After successful treatment of various pathological conditions with antiorgan sera (ACS) was reported by Russian investigators, interest in this subject was awakened in this country (see review of C. M. Pomerat, 1946; also Straus *et al.*, 1946).

*Material and methods.* The present report includes one phase of the study on the mechanism of action of antiorgan sera on the course of typhus and spotted fever in guinea pigs after intradermal inoculation into an area infiltrated with the serum.* This involves primarily the skin as the natural portal of entry and as dermal barrier for these infections. Similar technique was used as in previous investigations on the protective value of specific immune serum on spotted fever (Anigstein *et al.*, 1944). A square area (one centimeter along each side) on the guinea pig's abdominal skin shaved with a clipper is delineated and, after disinfection with soap and Zephiran solution, injected intradermally (needle ¼-inch long, 27 gauge) at 4 corners toward the center with the serum (0.1 ml. at each corner). The center of the infiltrated area is injected 2 hours later with 0.1 ml. of a 10% brain suspension of a typhus or spotted fever guinea pig. The antiorgan serum was prepared by repeated intravenous injections and oral administration of guinea pig spleen and bone marrow to rabbits according to the original technique of Marchuk (1943) and its modification (Anigstein *et al.*, 1947).

*The strain of louse-borne typhus was secured through the courtesy of Dr. John P. Fox, Laboratories of the International Health Division, Rockefeller Foundation, New York. This strain was originally isolated by the U.S. Typhus Commission during the typhus epidemic in Naples, Italy. The Rocky Mountain spotted fever strain was kindly supplied by Dr. R. R. Parker, Director, Rocky Mountain Laboratory, U.S. Public Health Service.

Each series of test guinea pigs was accompanied by controls, the latter injected intradermally as above with identical amounts of infective brain tissue only. Furthermore, parallel controls were treated with normal rabbit serum, followed by the infective inoculum. Both immune and normal sera were used in 1:5 and 1:10 dilutions, the injected amount totaling 0.08 ml. and 0.04 ml. of serum, respectively. In a series of tests the globulin fraction of an antiguinea pig serum (dilution 1:10) was used. The guinea pig antiserum known to contain the Forssman antibody was used in some experiments before and after absorption with sheep red cells. The same procedure was applied to those "normal" rabbit sera which showed antisheep cell lysins. The evaluation of the potency of the antisera *in vitro* was based on their complement fixation with the homologous antigen (spleen and bone-marrow) and by their action on the outgrowth of tissue explants. The latter tests were performed by the Tissue Culture Laboratory.

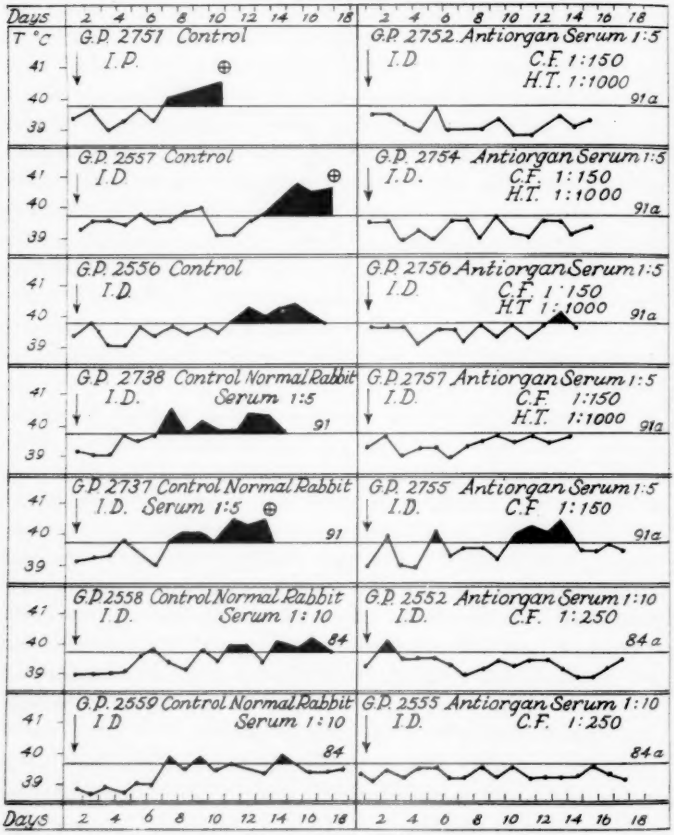
*Experiments and results.* Groups of 6 to 12 afebrile guinea pigs of both sexes (400–500 gm. body weight) were used in unit experiments in various combinations. The following are some unit experiments and their results: Of 6 guinea pigs in one series treated intradermally with guinea pig antiserum (1:10) and 2 hours later injected intradermally with typhus brain at the site of serum inoculation, 4 animals remained afebrile, in one the course of fthe disease was markedly attenuated, and one responded with typical typhus. All controls reacted with typical fever after 6 days incubation. Of 6 animals of another series 5 remained afebrile, while only one responded with fever of 2 days duration.

Significant results were achieved with antiguinea pig rabbit serum 91a (Complement fixation titer 1:150; hemolysin titer 1:1000) used in dilution 1:5. In this group of 5 guinea pigs, 4 remained afebrile and one developed fever after 11 days (Table I, 2755). It is of interest to note that the controls (Nos. 2737 and 2738) treated with the serum from the same rabbit obtained before immunization ("normal" serum) reacted with typical typhus (Table I). The same antiorgan

TABLE 1

## TYPHUS FEVER VS. ANTIORGAN SERUM

*Fever charts of guinea pigs inoculated intradermally with serum 2 hours prior to infection with rickettsiae*



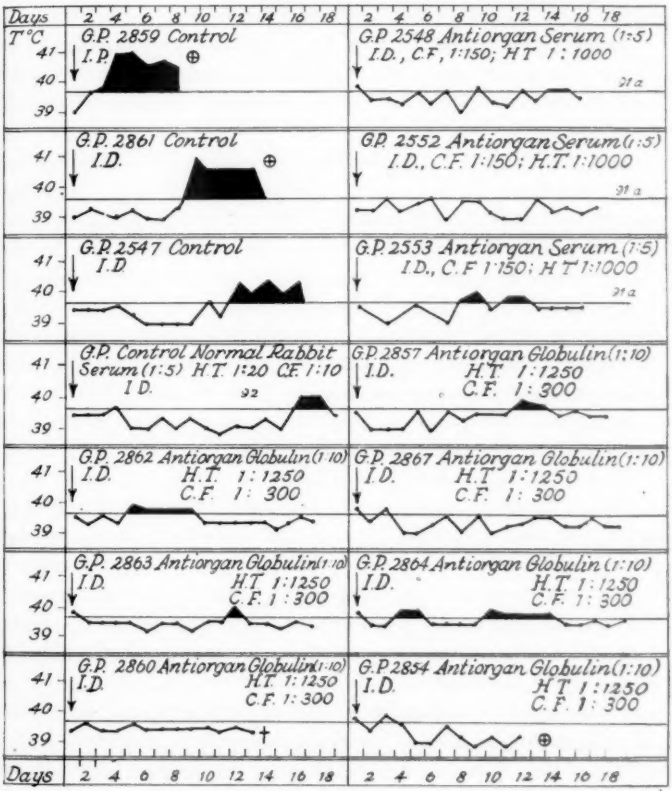

LEGEND: I.P. intraperitoneally
I.D. intradermally
C.F. complement fixation titer
H.T. hemolysin titer

serum 91a tested against spotted fever gave similar inhibition (Table II).

TABLE 2

**SPOTTED FEVER VS. ANTIORGAN SERUM**

*Fever charts of guinea pigs inoculated intradermally with serum 2 hours prior to infection with rickettsiae*




LEGEND:

I.P. intraperitoneally ⊕ Killed
I.D. intradermally
C.F. complement fixation titer
H.T. hemolysin titer † Died

In analyzing the control series it became evident that an attenuation of typhus fever can be achieved occasionally by sera of untreated rabbits. This is illustrated by guinea pigs Nos. 2558 and 2559 which showed atypical and abortive fever attacks. On the other hand, steady normal temperatures of guinea pigs Nos. 2552 and 2555 treated with the antiserum of the same rabbit (84a) were recorded.

Experiments with spotted fever included, in addition to native antiorgan sera, their globulin fraction, found to contain the active inhibitory factor of REIS (Frieden, Pomerat, Anigstein, 1945).

At first, infective guinea pig spleen was used as spotted fever inoculum at the site of the serum injection. Since the results were invariably identical with the untreated controls, it was assumed that a fixation of the splenic tissue in the skin by the homologous antiserum might be responsible for lack of protection. This antigen-antibody union in which, according to Hyde (1928), the intervention of the guinea pig complement is essential, may be compared with the phenomenon of invert anaphylaxis. This would apply to the homologous organ specific antibody reaction with the spleen as well as to the heterophile (Forssman) combination. However, no systemic reactions of the anaphylactic type were visible in guinea pigs treated with small amounts of the antisera. Similarly, except for a slight edema and sometimes perceptible induration of the injected area no skin lesions known to be produced by heterophile antisera were observed.

With the infective brain as intradermal inoculum the usual 3 to 4 day incubation for spotted fever was found extended to 7 to 10 days duration.

As observed occasionally in the typhus series, some of the normal rabbit sera also showed a suppressive action on the course of the disease. The serological analysis of these "normal" sera gave evidence of lysins against sheep cells and sometimes a complement fixation with guinea pig spleen as antigen. Hemolysin titers of 1:20 or 1:40 were not uncommon and in some cases were as high as 1:200. This has been recorded by other workers and attributed either to constitutional, genetic factors (Witebsky and Neter, 1935) or to past

infections of heterogeneous origin (Hyde, 1928). According to Witebsky and Neter (1935), normal rabbit sera containing heterophile antibody react with host cells which possess Forssman antigen (*e.g.*, guinea pig) and can display "primary toxicity." It is not improbable, therefore, that in our experiments the peculiarities of the "normal" rabbit sera play a role in the barrier effect of the skin. Attempts are being made to investigate the possible role of the hemolysins by absorption of the rabbit sera with sheep cells but the preliminary results suggest no significance. It may be added that certain normal rabbit sera have been observed to induce marked macrophage formation within 18 hours with strong phagocytic capacity in chick spleen explants. This phenomenon was found not correlated with rabbit sera of various hemolysin titers (C. M. Pomerat, personal communication).

Investigations are in progress on the role of complement in antiorgan serum. The importance of complement was recently re-emphasized by Maaløe (1947) in the promotion of phagocytosis. A similar analysis is in our case complicated by the fact that, unless complement-deficient guinea pigs are used the loss of complement in the antiserum will be supplemented by the tested guinea pig.

The experiments with guinea pig antiserum 91a which proved protective in typhus fever showed similar qualities when challenged with the highly virulent spotted fever. Abortive fever reaction was noted in guinea pig 2553 with no temperature rise in Nos. 2548 and 2552 (Table II). Similar reactions were observed in seven animals treated with the globulin fraction (used in dilution 1:10) of higher complement and hemolysin titers (1:300 and 1:1250). The same globulins diluted 1:100 gave no protection. Furthermore, no differences were noted *in vitro* in the action of original sera as compared with their globulin fraction on tissue explants (C. M. Pomerat, personal communication).

While the nature and mode of the action of the antiorgan sera are still obscure, the results can be compared with those previously reported when the specific antirickettsial rabbit immune serum was used against spotted fever (Anigstein *et al.*,

1944). This hyperimmune serum was produced by inoculating rabbits with commercial spotted fever vaccine followed by a final dose of living spotted fever rickettsiae in the spleen of the infected guinea pig (l.c.). Thus, in using the infective spleen as antigen, an antiorgan component was unintentionally introduced. In the light of the present study it is not improbable that this additional factor contributed to the protective power of the serum used in doses as minute as 0.025 ml. per guinea pig (l.c.).

## Discussion

The interpretation of the results involves a variety of factors among which are the barrier effect of the skin, the modified permeability of the connective tissues and the invasiveness of the rickettsiae. In emphasizing the physiological phenomena of the skin, the role of the reticulo-endothelial cells of the connective tissue and the phagocytic reactions should not be minimized. Reasoning from tissue culture experiments of C. M. Pomerat (1947), it may be that the induction of a macrophagic reaction is associated with a series of phenomena which alter the physiological state of the connective tissues thus preventing the spread of the infection.

The theoretical suggestions here advanced are under experimental study.

## Summary

Antiorgan sera were prepared by immunization of rabbits with guinea pig spleen and bone-marrow. A square area on the abdominal skin of the guinea pig is injected intradermally with 0.1 ml. antisera (1:5 and 1:10 dilutions) at 4 corners toward the center. After 2 hours, 0.1 ml. of a 10% brain suspension of typhus or spotted fever guinea pigs is inoculated into the center of the infiltrated area. The same procedure was adopted for normal rabbit sera in parallel control series. Protective properties against typhus and spotted fever, previously absent in the serum of untreated rabbits, were demonstrated in the sera from the same animals after their immunization with guinea pig spleen and bone-marrow.

However, an attenuation of the infection was noticed occasionally when serum of certain "normal" rabbits was used. Among the antibodies present in the antisera, two main groups were disclosed: the antiorgan antibodies and the heterophile (Forssman) antibodies. The serological analysis of "normal" rabbit sera revealed antisheep cell lysins in titers from 1:20 to 1:250. Preliminary tests suggest that hemolysins (Forssman) are not responsible for the inhibition of the rickettsial infection.

The authors make no suggestions as to the possibilities of utilizing the methods and results described as a practical application for protection against or treatment of typhus or spotted fever.

ACKNOWLEDGMENTS

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# NEWER CONCEPTS OF SCHIZOPHRENIA

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Modern psychiatric thought considers schizophrenia a group of related disorders manifest by apathetic, silly or unexpected emotional reactions with defects in the processes of thinking and reasoning, and in many instances the presence of delusional and hallucinatory phenomena. These cases were originally grouped together under the term, dementia praecox, by Kraepelin because he felt they shared the tendency to chronicity, the tendency to develop in early adult life, and the tendency to deteriorate. Schizophrenia was a term suggested by Bleuler, because he felt it more accurately described the breaking up of the normal patterns of response and also described the dissociative processes of thinking. Adolf Meyer proposed the term parergasia because he believed it still more accurately expressed the distortions in the behavior pattern seen in the patients suffering from this disorder.

The etiology of the schizophrenic reaction is unknown. Yet, in spite of this, less than one per cent of the public's money spent for the care of these individuals is devoted to research. At this moment, between 15 per cent and 20 per cent of the hospital beds in the United States are occupied by patients suffering from this one disease. The explanations for the cause of these reactions are many and are notable examples of the verbal dexterity of modern psychiatrists, but they have contributed very little to our developing a more satisfactory form of treatment for these patients. Kraepelin originally believed the disease was some type of inherited defect. This concept has been in a large measure discarded, and while there are cases which show a familial tendency, the observed frequency certainly cannot be described in terms of the Mendelian ratio.

The present theories can be classified into two large groups: (1) that schizophrenia is a faulty reaction pattern of life; that

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is, a type of functional disorder, and (2) that schizophrenia is an organic disease process of unknown cause and unknown pathology to which are added certain functional components.

The view that schizophrenia is a form of reaction to life situations, or a functional psychosis, has distinguished American psychiatry under the stimulation of Meyer, Hoch, White, Freud and their pupils. The basic thesis in this view is that certain persons are unable to adjust to the experiences dealt them by life and they adjust by withdrawing from active participation, or they work out a compromise that is unsatisfactory to both themselves and to the environment. A person confronted with this situation begins to find his satisfactions in phantasies where he says or does the things he wished he had done in the original setting. As time passes and these difficulties accumulate and his dissatisfaction with his adjustment to the world about him increases, the patient depends to an increasing degree upon himself and his phantasies for his pleasures and achievement. At last, this develops to a point where the patient is no longer able to distinguish between that which is real and that which is of his own creation. When this stage is reached, the patient may be said to be psychotic. His own ideas, beliefs, and wishes are assumed to be facts of the environment. This, of course, always results in difficulties in adjustment to families and to friends, neglect of his social obligations, his person, and his business.

The organic theories have been more popular in Europe. There is a vast amount of literature reporting various pathologic, physiologic, and chemical changes in schizophrenics. Unfortunately, in most of these cases the clinical psychiatric and the physiological studies are so poorly done, or at least so poorly recorded, that it is impossible to decide accurately whether or not the cases in the various series are altogether comparable. So-called body constitution or body type has been correlated with the development of schizophrenia, and while it is true that there are more linear, or asthenic, or leptosomatic body types among schizophrenics, it is also true that there are so many cases among persons of broad or athletic build that asthenic habitus cannot be said to be an essential to the development of schizophrenia. Pathology of the brain

has been reported by many laboratory workers. These findings have been in general nonspecific and have been found only in a certain proportion of all cases studied.

Recently, Penfield, Elvidge, and Reed have demonstrated a glial reaction in the white matter of biopsy specimens removed from both acute and chronic cases of schizophrenia. They believe that the symptoms of schizophrenia are due to some disturbance in the association pathways and report similar findings in manic-depressive patients and patients in post-epileptic stupor. They found no such changes in patients who were mentally clear and were suffering from epilepsy or other forms of neurologic disorders. Goldstein, Nissl, and Orton also found glial reactions in the white matter in the deep cortical layers, plus an increase in the lipoid content of the ganglion cells. Dunlap made a famous report of the pathological studies in schizophrenia in which he states: "First, the changes in the brain of schizophrenia are not only inconstant and nonspecific, but they are such as may be found in any series of controlled cases." This did much to discourage further pathologic studies for many years. Many workers, however, still believe that pathology is present and the attitude of Spielmeyer probably best sums up their attitude: "There are many changes in which the anatomic analysis has revealed no deviation from the normal. It does not appear justifiable, however, to conclude, as many investigators have done, that such a negative finding renders apparent the functional rather than the organic nature of the processes of dementia praecox."

There are also studies pointing to some type of metabolic disturbance in schizophrenia. Some of the most valuable of these have to do with what appear to be rather localized disturbances in metabolism; that is, disturbances in metabolism confined to the brain. Boon quotes Peters as follows: "Some of his observations (Peters') in cases of schizophrenia and dementia senilis and also in Lawrence-Moon-Biedl syndrome seemed to suggest degenerative alterations in the neurosecretory process of the autonomic cells (hypothalamic neurons)."

Ashby made interesting studies on the distribution of carbonic anhydrase. He reports on the distribution of the enzyme

in the cortex in normal human beings and in persons dying from various types of trauma and in persons dying from various types of mental disorder. He found that there is a specific type of deviation in the enzyme content of the brain in schizophrenia, and in paretics who had received long treatment without mental improvement; he found differences which appeared to be due to a deterioration in those areas which normally have a higher enzyme content.

Other studies show more generalized disturbances in brain metabolism in schizophrenia. Kraepelin long believed that the disease was due to metabolic autointoxication resulting from some disturbance in the gonads. Mott reported testicular and ovarian atrophy with attendant endocrine dysfunction and final brain pathology in schizophrenics. This work was severely criticized, and Morse pointed out that the changes were probably unrelated to schizophrenia. Recently Hemphill, Reese, and Taylor reported a special form of atrophy of the tubules of the testicles in many schizophrenic patients. They did not encounter these changes in control subjects or in patients suffering from other types of mental disorders. These studies were made on biopsy specimens taken from patients in good physical condition, and they found the atrophy varied in severity with the severity of the psychosis and did not vary with the duration of the illness, the patient's age or his body type.

Meduna has well summarized the literature on the disturbances in carbohydrate metabolism in schizophrenia and states that the evidence all points toward some type of disturbance in the enzymatic factors in the nervous system. Pfister, Gellhorn and others have presented evidence to show that there is some disturbance in the autonomic nervous system which they feel is the basic pathology in schizophrenia. Along these lines, Danziger has reported a survey made of compounds causing mental symptoms in man, and has found that all of these compounds have one property in common, which is that of interfering with the use of either oxygen or carbohydrate. Etiologic theories and findings in schizophrenia may thus be summarized that many patients show a disturbance in various structures and in various metabolic processes.

## Work in Progress

The remainder of this discussion would more properly be entitled "Not things we have done, rather things we are trying to do." Most of the papers in the literature report certain types of pathology, all of which occurs in only a certain percentage of the patients studied. It is our belief that the difficulty is that the cases represent a group of disorders and not one disorder, and that clinical studies are not reported in sufficient detail so that the patients may be divided into their proper category. We have been attempting to subject all of our patients to a very detailed clinical and laboratory study in an attempt to see if the patients showing various types of disturbance in physiology will not fall into certain groups or patterns. In collaboration with the tissue culture laboratory, which is part of the Galveston State Psychopathic Hospital, we are attempting to approach any possible constitutional differences in the cellular tissue in schizophrenia as opposed to that in other states.

Dr. C. M. Pomerat and his co-workers have been culturing brain specimens taken from living human beings, the material being derived from biopsy material taken at the time of craniotomy and ventriculography in patients suspected of brain tumor or in patients having a prefrontal lobotomy. Needless to say, the techniques involved in getting nerve fibers to sprout from adult human brain is quite difficult, but at this time we have had considerable success in getting these specimens to show good outgrowth of nerve tissue. Various compounds have been studied for their effect on the rate of growth of growing fibers cultured from chick embryo cord.

As soon as the technique for growing adult tissues is sufficiently standardized in a given media and the fibers will grow at a given rate, we can then investigate (1) whether or not there is a difference in the rate of growth of the control and schizophrenic tissue in a given media and (2) whether or not the control and pathologic material respond in different ways to various preparations. We believe that this is a new way of approaching the study of the metabolism in the nerve tissue of the schizophrenic patients and will add

another small fragment of information concerning the presence or lack of differences in these cases. All the cases from which the material is taken are carefully studied from a clinical point of view. The clinical studies are being set up in an effort to determine what particular pathology they show in the emotional and thinking sphere to correlate these with the rate of growth in response to the various media.

In the more purely clinical sphere, certain experiments are going forward. These are still very incomplete and the following material is offered only as an indication of what we are doing in the hope that it may stimulate others to participate in this study, making more data available in a shorter period of time. In these patients various types of compounds have been used which are known to be part of the normal carbohydrate metabolism in man. The reasoning behind this is (1) as pointed out earlier, all treatments that seem to influence schizophrenia in any way influence carbohydrate-oxygen metabolism in some manner and (2) the treatments cause some shift in the autonomic system toward the adreno-sympathetic side. It is possible to utilize only compounds that have been previously used in human beings for other disorders.

Glutamic acid was used in one of our series because it has been reported experimentally to increase the oxygen utilization in the nervous system, is known to be one of the steps in normal carbohydrate-oxygen utilization and has been shown to improve the physiologic performance of rats in maze running and to improve the psychologic performance of certain mental defectives in test situations. It was accordingly given to a series of 42 patients, which includes five patients so treated by Dr. Robt. Gilliland at the Veteran's Administration Hospital at Waco, Texas. The usual dosage was 12 gm. of glutamic acid per day. Of these patients, 19 were simple schizophrenia, 9 were paranoid schizophrenia, 5 were catatonic schizophrenia, 3 were hebephrenic and 4 were mixed types. One patient was suffering from Huntington's Chorea with psychosis and one showed a schizophrenic-like reaction in a mental defective.

In most instances in those showing improvement under glutamic acid therapy, it was temporary, but in others it was

prolonged and has been maintained to the present time. In all instances the improvement was an increase in the motor activity. It is interesting to note that those patients within this subgroup who were most affected were those patients whose symptoms were primarily characterized by apathy, complaints of weakness, fatiguability and lack of interest in their surroundings. In each instance, the improvement consisted in the patient showing a great deal of spontaneous activity, such as getting up out of bed, taking an interest in the ward activities. In two cases who had been bedridden for months, marked interest was shown in going outdoors and engaging in hard physical labor with the gardening crew. One patient who had been an apathetic catatonic schizophrenic for many months became extremely overactive, showing a rather typical catatonic excitement. Dr. Gilliland reports another patient who had been mute and catatonic for about fifteen years, as showing transient activity for about one week, then regressing. While it is true that these patients often shift from a catatonic to an excited stage, at least in these two instances it was coincident with the ingestion of glutamic acid.

The two patients in the paranoid group who showed improvement, had been badly deteriorated and quite apathetic, and the improvement, which was very slight, consisted entirely in becoming more interested in their environment and taking more interest in their personal appearance. The one patient in the hebephrenic group that showed any response at all to the treatment showed the same thing; that is, an increase in energy output. It is interesting to note that in the other patients other than schizophrenics who received the drug, the only one showing any improvement in behavior was the mental defective patient with psychosis, and her illness was also characterized by marked apathy, irritability and paranoid coloring not unlike that seen in simple schizophrenia. Her improvement also consisted of an increased output of energy.

More recently, through the courtesy of Dr. David Green of Columbia, we have availed ourselves of a small amount of Cytochrome C. This compound has been used by Proger, Dekasneas, and Schmidt in treating certain anoxic states such

as the anginal syndrome. We attempted to use this preparation in the treatment of schizophrenia but the results are still too early to be conclusive inasmuch as we administered this compound to only one patient, a catatonic schizophrenic who showed no change in her symptomatology. Because it is so difficult to obtain and to prepare, it will probably be some time before sufficient series can be run to decide whether or not this potent respiratory enzyme will in any way influence the symptomatology of schizophrenia.

Several references in the Russian literature refer to the use of antireticular-cytotoxic serum (ACS) or so-called "Russian Serum" in psychiatric practice, indicating that it has a favorable effect in certain psychoses, particularly schizophrenia. The rationale for the use of this preparation is not clear in the Russian literature that we have been able to find or to translate, the only explanation being this statement: "Its therapeutic effect on schizophrenia caused by disorders of the microglia and of ozena indicated the trophic effect on the connective tissue." This statement is not quite clear to us, but in attempting to figure out a rationale for our own benefit, other than the fact that the Russians had reported beneficial effects, we reasoned as follows: The work of Penfield, Elridge, and Reed indicate that schizophrenia in some instances at least is accompanied by an increased glial response in the central nervous system. If one assumes that this glial response is the organism's reaction to the basic pathology in schizophrenia, then one might postulate that the stimulation of the reticuloendothelial system by this serum might be of some benefit in this disorder. It is also interesting to remember that Ashby's work showed the shift in the presence of certain respiratory enzymes in approximately the same areas in which Penfield, Elvidge, and Reed found the increased glial reaction.

Using this as our rationale and having assurance that the preparation is apparently harmless in human beings, we have at this writing administered the material, reticuloendothelial immune serum, to ten patients. For the sake of brevity, no case histories will be presented, but each patient was subjected to a complete physical, neurological, psychiatric, psychological,

and laboratory examination previous to administration. Doctor Pomerat, of the Tissue Culture Laboratory prepared and supplied this serum and aided in the laboratory studies. The serum was administered intramuscularly to all patients in dosages from 0.5 cc. of 1:10 dilution for the first dose; 1 cc. four days later; then 1.5 cc. two days later. Zalkind and Chernobrovkina recommended four modes of administration. First, they recommended one course of ACS alone; second, one course of ACS followed by additional types of therapy; third, one course of ACS and approximately one month later a second course; and fourth, one course of ACS with additional therapy, followed by a second course. In our own series, eight of our patients had already been treated by a combination of both electroshock treatment and insulin shock treatment without any appreciable benefit before ACS was administered, the smallest number of electroshock treatments being sixteen and the largest number thirty-six, the smallest number of insulin comas being six and the largest number fifty-two. One patient received two courses of ACS as recommended by the Russians before any other type therapy was instituted. One patient who received one course of ACS before any other type therapy apparently received no benefit from that, but responded satisfactorily on ten electroshock treatments. Of the ten patients, five received two courses and five received only one course. In two instances of the simple retarded type of schizophrenia patients, there was some temporary reaction in terms of increased effort. However, in all instances these reactions were so minimal it was felt that they were not clinically significant. In no instance was there any complication except considerable swelling and redness occurring at the site of injection. No appreciable changes were noted in the red blood count, hemoglobin, sedimentation rate, volume packed cells, clotting time, or the white cell count and differential except the counts taken coincident with the local reaction at the site of injection. No changes were noted in the electroencephalogram tracings following, as compared to those prior to, the administration of this preparation. Neither was there any significant variation in the Rorschach or Minnesota

Multiphasic Test given before and after the administration of ACS.

Further experiments with this material are being done, but the present indication is that it is of little benefit. The tissue culture laboratory has felt that perhaps some more specific stimulating serum was indicated and has recently succeeded in preparing an anti-brain serum, but as yet this has not been tried in human beings.

The studies above report our fumbling efforts at some research and investigation into this disorder. A detailed report of these studies, with methodology and analysis of results must await more conclusive evidence. This is merely an in-the-family announcement of a study in progress. If this will stimulate anyone to start similar studies here or elsewhere, it will have served its usefulness.

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# THE EFFECT OF VARYING HYDROGEN ION CONCENTRATIONS UPON THE STABILITY OF HEATED FRUCTOSE SOLUTIONS

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## INTRODUCTION

In an effort to determine the practicability of using hydrolyzed sucrose solution for intravenous infusion in medical and surgical practice, this laboratory undertook to determine the nonsugar decomposition products which are formed during the hydrolysis of sucrose at varying concentrations of acid used for the hydrolysis and different concentrations of alkali which may result at least temporarily in the neutralization of the solution. The fact that the behavior of glucose in solution with varying amounts of acid and alkali is comparatively well known prompted us to concentrate our attention on the fructose fraction of the invert sugar.

A preliminary survey of the literature indicates that the physiological action of fructose differs somewhat from that of glucose. Deuel, Guleck, and Buth state that fructose in 50–70 gram doses is effective in diminishing ketosis when administered by mouth to human subjects who have been maintained on fat and protein diet. Brown *et al.* on the other hand have shown that fructose is distinctly less effective in the treatment of insulin shock in dogs than is glucose. Takizawa states that it is possible to induce sarcoma in rats by the subcutaneous injection of 0.75 ml. of 25% fructose. Since, however, at least 100 injections were necessary for the production of neoplasia, the factor of repeated and indiscriminate irritations must be borne in mind.

Certain Russian workers have shown that fructose can be the substrate for the formation of lactic in the blood as well as in the central nervous system. In this respect as well as in many others, the metabolism of fructose does not differ

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significantly from that of glucose. In the intact animal fructose appears to be rapidly converted into glycogen by the liver; therefore some of the apparent physiological properties of fructose may be, in fact, those of glucose which is formed from the fructose by the liver and other tissues of the animal. At this time our immediate interest is to learn how much fructose may be changed into "non-sugars" under conditions which may be used to convert sucrose into invert sugar and to ascertain, at least to some extent the nature of these compounds.

## Procedure

Solutions of fructose in concentrations of 10% were placed in an autoclave and heated for a period of 20 minutes at pressures from 10–15 psi and temperatures from 116°–118° C. Prior to autoclaving the pH was carefully adjusted using hydrochloric acid and buffers. Subsequent to autoclaving, the solutions were removed and cooled, and a minute quantity of thymol was added to prevent bacterial fermentation. The main line of investigation was concerned with determinating the amounts of sugar left undecomposed by the sterilization. This was done by three kinds of analysis. First, polarimetric determinations were run on all samples, using a Schmidt and Haensch polarimeter, light of wave length 606–573 uu. and 20 cm. polarimeter tube. When the color of the solution had darkened perceptibly as occurred at pHs over 4–5, ten cm. tubes were used and the results extrapolated. In one case it was necessary to decolorize the solution with Norit charcoal powder before analysis could be made. Since the darkening of the solutions was due to carbonization, little if any of the optically active components were removed by the decolorization procedure. Second, the reducing power of the solutions was determined using the method of Somogyi. Third, a specific determination for levulose was made by the colorimetric method of Roe using a Klett Summerson photelometer. In all cases blank determinations on unsterilized samples of sugar were run. Also blanks were run to determine the effect, if any, of the buffers used, and also of the thymol.

Besides this main line of investigation, specific analyses were run to determine the quantities of decomposition products

formed. Since the greatest amount of decomposition took place at the lowest pHs, most determinations were made on samples in this range. The furfuraldehyde was determined according to the method of Leach modified to our particular needs. Forty cc. of the solution were extracted with ether in a separatory funnel. This extract was then treated with 0.25 gms. of phloroglucinol in 12% HCl and permitted to stand for 24 hours. The phloroglucinol preparation was filtered, washed, dried at 100° C. for one hour and then weighed. The amount of furfural was then calculated according to Leach's formula:

$$F = 0.517\ (X + .0052)$$

where $X$ = wgt. of precipitate
$F$ = wgt. of furfuraldehyde

The analyses for levulinic acid were made by the $\beta$-naphthyl hydrazine method. Briefly this method consists of evaporating 20 grams of the solution to dryness, then adding tartaric acid and anhydrous sodium sulfate and triturating. This mass is then transferred to a stoppered bottle and 100 cc. of ether are added. Fifty cc. of this are taken after filtration and evaporated. A sample titration is then run with sodium hydroxide to determine the approximate theoretical amount of $\beta$-naphthyl hydrazine to be added. The $\beta$-naphthyl hydrazine is then added and allowed to stand at room temperature for four hours. The precipitate is then water washed, dried again for three hours at slightly lower temperatures and weighed. The weight of levulinic acid is calculated from the following formula:

$$\text{Levulinic acid} = X(0.453) + 2 \text{ mg.} + (0.35 \text{ mg.} \times V/10)$$

where X is the weight of the precipitate in grams and
V is the volume of wash water in ml.

The determination of heterolevulosan was delayed by the necessity of preparing some of the pure compound according to the method of Pictet and Chavan. This method consists of dissolving 100 grams of fructose in 400 grams of hydrochloric acid (sp. gr. 1.2) and permitting it to stand for 72 hours at 0° C. Subsequently, the acid is drawn off by evacuation. The remaining acid is neutralized with lead carbonate.

The resulting lead chloride is removed with silver carbonate and the silver salts removed by precipitation by hydrogen sulfide. To the remaining solution brewer's yeast is added and the solution is kept at 35° C. for 10 days. The solution is then boiled with calcium carbonate to neutralize the acids formed during the fermentation period. The carbonates are then filtered off, the solution is evaporated to dryness and the residue redissolved in warm methyl alcohol.

After preparation of the pure product, the analysis was done according to the method of Hestrin *et al.*, which consists of precipitating the heterolevulosan with ethanol. The precipitate is then centrifuged, filtered off, and redissolved in boiling water. This procedure is repeated two more times and the filtered precipitate is then dried and weighed.

FIG. 1

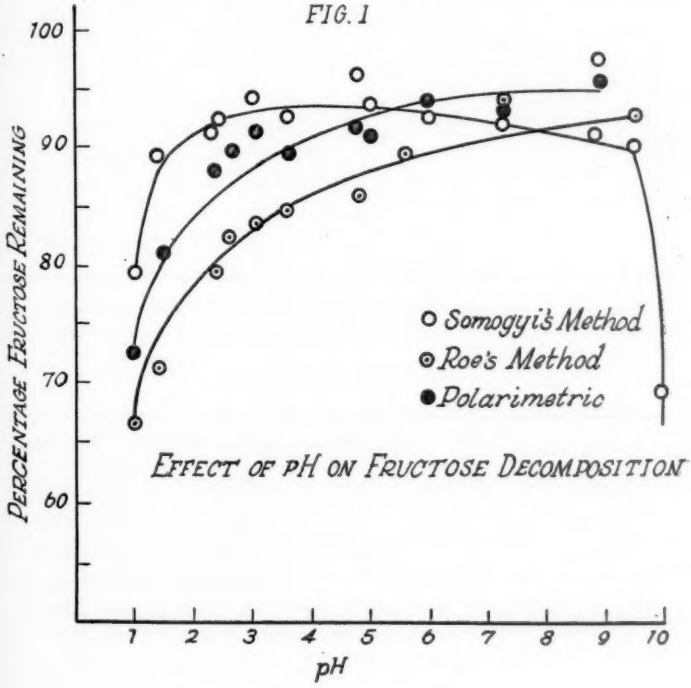

TABLE I

| Sample No. | Beginning pH | Temperature | Autoclave Pressure | Percentage of Sugar remaining | | |
|---|---|---|---|---|---|---|
| | | | | by Somogyi method | by Roe method | by Polarimetric method |
| | | °C. | lb. per sq. in. | % of orig. | % of orig. | % of orig. |
| 1 | 1.0 | 116 | 10 | 7.92 | 6.67 | 7.24 |
| 2 | 1.4 | 118 | 15 | 8.95 | 7.10 | 8.12 |
| 3 | 2.3 | 116 | 10 | 9.10 | 7.90 | 8.74 |
| 4 | 2.4 | 118 | 15 | 9.30 | 8.25 | 8.97 |
| 5 | 3.0 | 118 | 15 | 9.40 | 8.37 | 9.24 |
| 6 | 3.7 | 116 | 10 | 9.32 | 8.44 | 8.95 |
| 7 | 4.8 | 116 | 10 | 9.60 | 8.60 | 9.30 |
| 8 | 5.0 | 118 | 15 | 9.38 | ..... | 9.10 |
| 9 | 5.6 | 118 | 15 | ..... | 8.97 | ..... |
| 10 | 6.0 | 116 | 10 | 9.25 | ..... | 9.45 |
| 11 | 7.3 | 118 | 15 | 9.24 | 9.44 | 9.24 |
| 12 | 8.8 | 118 | 15 | 9.10 | 9.76 | 9.53 |
| 13 | 9.5 | 118 | 15 | 9.00 | 9.25 | ..... |
| 14 | 10.0 | 118 | 15 | 6.92 | 3.96 | ..... |

These values are relative, being based on blanks run simultaneously on untreated fructose solutions. The actual values of these blanks is as follows:

TABLE II

| Sugar | pH | Treatment | Analytic Method | Percentage |
|---|---|---|---|---|
| Fructose | 7.0 | None | Somogyi | 9.76 |
| Fructose | 7.0 | None | Roe | 9.60 |
| Fructose | 7.0 | None | Polarimeter | 9.70 |

The samples in Table I were all run for twenty minutes in the autoclave. The indicated pressures and temperatures were maintained as closely as possible.

## Discussion

A comparison of our determinations of fructose in solutions treated as described above shows some interesting variations. The data is given in Table I, and Figure I presents these results in graphic form. The determinations by the polarimetric and Somogyi's methods agree fairly well. Some considerable variations occur in the more acid and alkaline ranges. It is known, of course, that fructose as well as other simple sugars are rapidly destroyed in solutions which have a hydrogen ion concentration lower than neutrality. When the pH was above 8.5 the fructose solutions became dark and satisfactory reading could not be made with the polarimeter; but these results do show the rapid destruction of fructose at the higher pH levels. Those solutions which were treated at pH ranges from 3 to 5 showed minimal changes in concentration as determined by the polarimetric as well as by Somogyi's method. This finding is in substantial agreement with the results reported by Jackson and Mathews. Below pH 3 there is a more or less decrease in the stability of the fructose solutions. The decrease in optical properties of the solution is not exactly parallel to the decrease in reducing power of the solution as shown by our determinations with Somogyi's method. The decrease as shown by these two methods is quite marked and essentially equal at pH = 1.

Using the constants given by Mathews and Jackson we have calculated by means of Arlenius's equation:

$$A = \frac{2.303\ T_1\ T_2}{T_2 - T_1}\ (\log \frac{1}{KT_1} - \log \frac{1}{KT_2})$$

The velocity constant for 116° C. and pH 1. The value obtained is $2.43 \times 10^{-3}$. This differs only slightly from the value obtained by Mathews and Jackson. They found 1% decomposition in 6.8 minutes at 100° C. at pH 1. Since the reaction rate in this case increases 5 to 10 times for every 10° increase in temperature, the time required for 1% decomposition would be less than 1 minute under our conditions.

Figure I shows that the determination of fructose by Roe's method gave results which differ very considerably from those

obtained by the polarimetric and Somogyi's methods. The results of the three methods agree only at pH of about 7.5. The results obtained by Roe's method would indicate a much greater decomposition at pH 1–4 than by the other methods. We believe there must be some significance in these results but there is nothing in our data which would indicate the cause of this variation. It is possible that some substance is formed by heating fructose at pH 1 to 4 which even in small amounts inhibit the development of the colored compound upon which the method depends. These results do suggest that Roe's method from fructose may give unsatisfactory results under certain conditions.

TABLE III

| Substance | Method | Percent |
|---|---|---|
| Fructose | Roe | 66.70 |
| Reducing sugar | Somogyi | 79.20 |
| Levulinic acid | Bulir | 1.29 |
| Furfural | Leach | 0.18 |
| Unidentified | (by difference) | 19.33 |

Table III gives some idea of the products formed when fructose is heated at 116° at pH 1. It will be observed that most of the decomposition products have not been identified, but small amounts of levulinic acid, furfural and heterolevulosans have been found.

The hydrolysis of sucrose by acid has been studied by many workers and many results have been obtained which indicate that greater or lesser amounts of the resulting hexoses may be destroyed by this method of hydrolysis. This decomposition indicates that if invert sugar prepared from sucrose is to be used for intravenous injection, the solutions injected may contain more or less of the products of the decomposition of fructose. There is no evidence at this time that these products will be harmful. In fact we have injected intravenously carefully prepared invert sugar solutions into rabbits without obtaining any detectable unfavorable reaction. Moreover, we

have been able to give larger doses by mouth of levulinic acid to rabbits without any unfavorable reaction. This was true even after at least six daily doses of 10 grams each. We have injected rabbits with furfural also. In this case our results are neither so extensive nor so conclusive but we are justified in stating that any amount of furfural produced in the preparation of invert sugar would be entirely without harmful effect. The fact remains, however, that invert sugar solutions do contain small amounts of organic compounds in addition to glucose and fructose.

## Conclusion

It has been found that a fairly wide pH range exists over which fructose can be autoclaved without extensive decomposition. This range has its peak between pH of 3 and 5.

Below pH 2 and above 8 drastic reductions occur in the amount of fructose, and especially with considerable rapidity if the temperature is raised to, or above, the boiling point. Formation of levulinic acid, furfural, and heterolevulosan are shown to occur.

Velocity constants for the reaction at temperatures of 116° C. differ very slightly from those at 100° C.

The effect of these results upon the preparation of invert sugar solution for intravenous injection is discussed.

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# NITROGEN MUSTARD IN THE TREATMENT OF HODGKIN'S DISEASE: A CASE REPORT WITH DISCUSSION*

Case presentation on July 30, 1947, by Dr. George Tipton on Tumor Clinic No. 225: A white male 16 years old was admitted to the John Sealy Hospital on 26 Sept. 45 with a complaint of a swelling in left side of neck first noticed following mumps 3 years previously. The mass was discrete, about the size of a hen's egg, and had always been asymptomatic. There had been no weight loss, cough, malaise, night sweats or other evidence of fever. The body is otherwise free of swellings. No history of exposure to tuberculosis; patient drank raw milk until two years before admission. His grandfather died of skin cancer.

Physical Examination: Temperature 98.6° F.; pulse 76; respiration 20; blood pressure 115/75. A well developed, well nourished, hypersthenic individual who does not appear ill. The examination reveals nothing abnormal except a tumefaction in the left side of neck. The non-tender mass is firm and discrete, measures 3 x 4 x 5 cm., lies beneath the sternocleidomastoid muscles, is non-fluctuant, and does not pulsate. Several smaller masses are palpable in a chain in the posterior triangle of the neck and one in the submandibular region. The trachea is deviated to the right. Generalized lymphadenopathy is not present. No abdominal masses palpable.

X-ray examination of the chest reveals no abnormalities except deviation of trachea to right in neck. Laboratory Examination: Wasserman reaction: negative; sedimentation rate: 27 mm.; urine examination: negative; blood: RBC 4.1M; 12.2 hemoglobin; WBC 9,250; 48 segmenters, 7 stabs, 36 lymphocytes, 4 monocytes, 4 eosinophiles, 1 basophil.

On 1 Oct. 45 a small cervical lymph node on left was excised and examined microscopically to reveal the following: reticuloendothelial hyperplasia with loss of nodal architecture, occasional Reed-Sternberg cells and many eosinophiles. Diagnosis: Hodgkin's disease.

*From the records of the Tumor Clinic Conferences, John Sealy Hospital, The University of Texas Medical Branch, Galveston.

9 Oct. 45: Roentgen therapy given—200 r. daily to left side of neck for five days for a total of 1,000 r. Mass disappeared rapidly and patient was dismissed from hospital 16 Oct. 45.

28 Feb. 47: Readmitted to hospital. Mass in neck had reappeared and increased in size during past year. No weight loss. Temperature varied from 100 to 102. The neck felt stiff and enlarged; tender nodes in both axillae and in the left epitrochlear region. The liver extended 4 cm. below the costal margin and a tender spleen was palpable. X ray of the chest was negative. Blood: RBC's 2.54 M., hgb 52%; WBC's 8,100, 80 segs., 2 stab., 11 lymph., 6 mono., 1 baso. BSP test normal. Cephalin flocculation 3+ in 48 hours. Sternal puncture showed a slightly hypocellular marrow with a perceptible left shift in myeloid series.

A lymph node removed from the left cervical chain showed only chronic lymphadenitis.

Between March 13 and ?, 1947, 6,900 r. of X-radiation was given over both cervical regions and to the abdomen. The temperature slowly returned to normal and the patient was dismissed 9 April 47 having received numerous transfusions.

Fever with chills recurred about one week before readmission to hospital 30 June 47. Temperature now as high as 105. Patient appeared acutely ill, had abdominal pain, both liver and spleen tender and palpable, and he had lost 18 pounds. Chest still clear to X-ray. RBC's 2.3 M., 42% hgb.; WBC's 2,550, 62% segmenters, 3% stabs, 33% lymphocytes, 2% monocytes.

X-radiation, 3,600 r., to abdomen between 16 and 22 July was discontinued because blood count could not be maintained by repeated transfusions. WBC's 2,300. Jaundice had developed and fever continued 104 to 105.

## Discussion

*Dr. Martin Schneider:* To date, radiation therapy is the method of choice in therapy of lymphoma, including Hodgkin's disease. It is hoped that further development of chemical agents may yield a better salvage rate than the nitrogen mustards thus far used. They have at least won a place as a

supplementary weapon for the patient whose lesions have become radio-resistant, and some of these have apparently reverted to radiosensitivity after a course of mustard therapy. Unfortunately their action is not selective enough—in fact, less so than that of ionizing radiations which can at least be localized anatomically.

This patient has progressed from a relatively benign type of Hodgkin's in 1945, clinically limited to the neck and radiosensitive, to a paragranulomatous and possibly even a sarcomatous type in 1947. He returned to us only after a year of obvious recurrence had elapsed, thereby wasting valuable time; he now displayed a generalized disease with the febrile component and anemia so characteristic of abdominal and/or mediastinal involvement.

Radiation to the neck and abdomen caused a temporary remission in March, 1947; it is noteworthy that no evidence of hematopoietic injury is found in comparing the pre-radiation blood picture with that in July, 1947. Only the total WBC was decreased, with increase in lymphocytes, which are the most radiosensitive of all blood cells, and therefore should display the sharpest decrease in radiation damage.

We favor replacement of X ray by nitrogen mustard therapy at this time because the disease is definitely radioresistant now.

*Dr. Edgar J. Poth:* In view of past experience it might be well that this patient be given nitrogen mustards in the hope of inducing a remission and possibly again rendering the neoplasm sensitive to X-radiation. The disease is now widespread and nothing short of general systemic treatment can check its growth. If the patient can tolerate the drug it should be given for eight days in a daily dosage of 0.1 mgm. per kilo of body weight together with penicillin for protection against infection because the WBC's will be reduced even further. The danger due to the suppression of the bone marrow by the drug is even greater now, because it is already damaged by the radiation and cannot recover as rapidly as when only the drug is given.

*Reviewed at Tumor Conference Dec. 1, 1947.* Presentation by Dr. George Tipton: 1 Aug. 47: 5.0 mgm. of nitrogen mus-

tard given intravenously daily for eight days. Penicillin 50,000 U., I.M. q. 2 hr. Therapy caused nausea and vomiting for the first few days. After four days the abdominal pain disappeared, then the spleen became smaller, appetite returned and by the end of the course of therapy he felt much stronger. Temperature returned to normal in 12 days and there was a gain in weight.

The following table shows the leucocyte count as low as 750 during the third week after starting the treatment. During the next week the blood picture improved rapidly. (See Table I.)

TABLE I

The Variation of the Cellular Elements of the Blood During the Administration of Nitrogen Mustard

| Date Aug. | WBC per cmm. | PMN | Stabs | Eosino-Phils | Lympho-Cytes | Mono-Cytes | Platelets per cmm. | RBC M/ cmm. | Hb.-gms/ 100cc. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 3,500 | 49 | 8 | | 23 | 11 | 200,800 | 5,020 | 17.0 |
| 4 | 2,400 | 76 | 7 | | 6 | 2 | 254,280 | 4,890 | 15.9 |
| 6 | 4,000 | 90 | 1 | 1 | 5 | 3 | 375,560 | 4,590 | 15.4 |
| 8 | 2,100 | 91 | 5 | | 2 | 2 | | | |
| 11 | 1,100 | 70 | | | 28 | | 154,000 | 4,560 | 14.6 |
| 14 | 1,250 | 76 | 4 | | 16 | 4 | 160,320 | 5,010 | 16.8 |
| 18 | 850 | 24 | | 4 | 56 | 16 | 57,200 | 5,200 | 16.3 |
| 19 | 750 | 44 | 16 | 4 | 24 | 12 | 20,360 | 5,090 | 16.8 |
| 20 | 800 | 24 | 8 | | 64 | 2 | 32,760 | 5,460 | 16.8 |
| 21 | 800 | 28 | 8 | | 48 | 8 | 11,120 | 5,560 | 16.8 |
| 23 | 1,850 | 20 | 20 | 8 | 24 | 12 | 15,510 | 5,170 | 16.8 |
| 25 | 3,300 | 15 | 2 | 2 | 69 | 1 | 75,600 | 5,040 | 17.2 |
| 26 | 4,600 | 9 | 3 | 2 | 78 | | | | |

This remission was short lived and by 26 Sept. chills, fever, weakness and abnominal pain had returned with a plateau type of sustained fever between 102–105. Liver and spleen 3 and 6 cm. below costal margin, respectively, and X-ray

examination of chest showed a superior mediastinal mass and increased lung root shadows.

Beginning 20 Oct. small doses of X-radiation were given over body, but this was abandoned on the 29th after only 125 r. had been given.

Many transfusions had been given: RBC's 3.05 M.; WBC's 1,350, PMN 74%, Lymph 22%, Mono 2%, primitive chosmocytes 2%, platelet count 85,400.

The patient steadily lost ground, became stuporous, and was released from the hospital 7 Nov. 47 at the request of his parents. He expired 12 Nov. 47.

## Discussion

*Dr. William C. Levin:* This patient's hematologic course has been quite characteristic of a fulminating type of Hodgkin's disease. Within the four or five months that the patient was observed by us prior to the institution of nitrogen mustard therapy, the peripheral blood count showed a marked change. A moderate leucopenia and a moderately severe normochromic anemia became evident, although there were no other significant changes. The marrow changed little. If anything, there developed a hypercellularity. Another consideration must be borne in mind, however. It is possible that the deep X-ray therapy, which the patient had received, at least partially contributed to the development of the anemia and leukopenia.

Within nineteen days after nitrogen mustard administration was begun, the leucocyte count dropped to 750, and the platelet count to 11,000. However, a week later, the leucocyte count had risen to control levels, and a few days later, the platelet count had risen to above a critical level. During this time, attempts were made to aspirate marrow from the sternum, but no clumps were obtained. This probably reflected the transient hypoplasia of the marrow. A later marrow aspiration revealed only slightly hypocellular marrow. By this time, however (two months later), there was evidence of invasion of the marrow by multinuclear cells characteristic of Hodgkin's disease.

Now that we are able to treat tumors chemotherapeutically, I feel we should pursue the problem very energetically. It is certainly true that the present form of nitrogen mustard is not selective enough. Its chief toxic effect is exerted on the marrow, but we do have methods available to us to combat this effect. The anemia can be readily managed with blood transfusions, and the leucopenia usually produces no untoward effects as long as adequate doses of penicillin are administered to the patient. We do risk a great deal in producing a thrombocytopenia, since little can be done for the patient if hemorrhages become severe. The evidence so far available also suggests that marrow depression so induced is reversible. Regeneration of the marrow almost always develops shortly after the drug is stopped. It, therefore, seems to me that we should employ this method of treatment intensively in the hope that some encouraging information may be derived from our experience. It is, of course, absolutely essential that such patients be carefully followed hematologically during the course of therapy and that proper measures be taken to offset the toxic effects of the drug.

*Dr. Poth:* Probably, in the face of such a hopeless condition, nitrogen mustard therapy should have been given again, and in the event of another remission a smaller dosage schedule inaugurated in the hope of maintaining the benefit for a prolonged period. This procedure is being followed at present with a patient admitted with Hodgkin's disease in terminal stage with fever to 105–106 and apparently moribund. After inducing a remission, the patient has been maintained during the past month by daily injections of 0.05 mgm. of the drug per kilo of body weight. The patient is afebrile, ambulatory, appetite good, and wants to go home. We know from past experience that the remission will be brief if the drug is discontinued after the usual course of therapy, and it is hoped that prolonged therapy will give a lasting effect before there is prohibitive damage to other tissues.

## Calling Attention To:

### Items of Possible Interest to Friends of Our Effort
### Brave New Year: January, 1948

1. New Books: Henry Schuman announces several honies: Ruth Benedict and Gene Weltfish's *In Henry's Backyard: The Races of Mankind* (N.Y., '48, $2.50); D. Schullian and M. Schoen's *Music and Medicine* (N.Y., '48, 500 pp., $6.50); Dorothea Singer's *Giordano Bruno: His Life and Thought* (April, '48); G. Sarton's *The Road to Understanding: Essays in the History of Civilization* (April, '48), and D. Drake's *Pioneer Life in Kentucky*, ed. E. F. Horine (April, '48). F. S. C. Northrop discusses *The Logic of the Sciences and the Humanities* (Macmillan, N.Y., '48, $4.50). E. H. Northey summarizes *The Sulfonamides and Allied Compounds* (Reinhold, N.Y., '47, 688 pp., $15). M. Sahyun describes *Proteins and Amino Acids in Nutrition* (Reinhold, N.Y., '47, 540 pp., $7.50). I. Chavez surveys *Mexico en la Cultura Medica* (Colegio Nacional, Mexico, D.F., '47, 187 pp.). K. O. Moller offers *Pharmakologie als Theoretische Grundlage einer Rationellen Therapie* (Schwabe, Basle, '48, 744 pp., SwFr 48). K. von Neergaard discusses *Dynamische Reaktionspathologie* (Schwabe, Basle, '47, 320 pp., SwFr 24). H. A. Kreis compiles *Kompendium der Parasitischen Wümer im Menschen* (Schwabe, Basle, '47, 136 pp., SwFr 10). H. Standinger writes on *Makromoleculare Chemie und Biologie* (Wepf, Basle, '48, 160 pp., SwFr 18). Grace Crile edits Geo. Crile's *Autogiography* (Lippincott, Phila. '47, 2 vols., 640 pp., $10). L. V. Ackerman and J. A. Regato offer *Cancer: Diagnosis, Treatment, Prognosis* (Mosby, St. Louis, '47, 1200 pp., $20). R. T. Johnstone appraises *Occupational Medicine and Industrial Hygiene* (Mosby, St. Louis, '47, 550 pp., $8.50).

2. Biochemical: N. B. important symposium on *Nucleic Acid* (Symp. Soc. Exp. Biol. No. 1, Cambridge Univ. Press, '47, 290 pp., $8.50, 19 contributors: P. C. Koller concludes chemicals may be as effective mutafacient agents as ionizing radiation). E. Baldwin emphasizes *Dynamic Aspects of Biochemistry* (Macmillan, N.Y., 547, 480 pp., $4). Annual Review of Biochemistry increasingly stresses clinical applications (Annual Reviews, Stanford Univ., '47, 740 pp., $6). P. Karrer and R. Schwyzer consider possibility of antibodies against vitamins (*Helv. Chem. Acta* 30: 1767/47). O. Osler and Co. synthesize vitamin A derivatives (*Ibid* p. 1911). *The Chemistry of Penicillin* prepared under auspices of National Academy of Sciences and OSRD will be published by Princeton Univ. Press: see "Biosynthesis of penicillins" (*Science* 106: 503, Nov. 28/47). I. L. Chaikoff & Co. show thyroids fix inorganic iodine independently of subsequent conversion to diiodotyrosine and thyroxine (*J. Biol. Chem.* 171: 189/47). E. L. Smith and R. D. Greene find high threonine content (7–11%) in immune proteins (*Ibid.* p. 355). M. W. Chase continues

studies on sensitization by simple chemical compounds (*J. Exp. Med.* 86: 489/47). J. C. Barsantini and G. M. C. Masson say most sex hormone steroids inhibit lactation, via ovaries, while progesterone and adrenocortical steroids are inactive (*Endocrinol.* 41: 299/47). G. B. Wislocki continues studies on anatomical chemistry (molecular architecture of cells): for blood (*Anat. Rec.* 96: 249/47); for mammary gland (*Am. J. Anat.* 81: 309/47). V. S. Matthews & Co. report degenerative kidney damage after repeated administration of diethylstilbestrol and sesame oil (*Proc. Soc. Exp. Biol. Med.* 66: 195/47). E. R. Trethewie notes deaminating enzyme liberated from ischemic muscles (*Austral. J. Exp. Biol. Med. Sci.* 25: 291/47).

3. PHYSIOLOGICAL: J. F. Fulton, T. G. Brown and A. D. Ritchie eulogize C. S. Sherrington on his 90th birthday (*Brit. Med. J.* 2: 807–813, Nov. 22/47). G. Ekehorn continues penetrating study of G. S. Sherrington's philosophy in manner as stimulating as his subject (*Acta Med. Scand. Suppl.* 199, Stockholm, '47). J. Beattie well reviews metabolic disturbances after injury (*Brit. Med. J.* 2: 813, Nov. 22/47). B. D. Wyke reviews clinical physiology of the cerebellum (*Med. J. Austral.* 34: 2: 533, Nov. 1/47). F. Brucke surveys physiology and pharmacology of the thyroid (*Wien Klin Wchsch.* 2: 709, Oct. 31/47). M. Monnier and F. Boehm describe perimetric electroretinography (*Hely Physiol. Pharmacol. Acta* 5: 205/47). J. F. P. Erasmus notes post-traumatic arterial spasm (*South Africa Med. J.* 21: 806, Nov. 8/47). M. Wilburne & Co. recommend atropine for prevention of paroxysmal ventricular tachycardia (*Am. Heart J.* 34: 860/47). Our O. W. Beard and G. M. Decherd note variations in 1st heart sound (*Ibid.* p. 809).

4. NEW YEAR NOTES: N.B. H. H. Dale's great Pilgrim Trust Lecture, The Freedom of Science (*Proc. Am. Philosoph. Soc.* 91: 64/47). N.B. L. Szilard's public letter to Stalin (*Bull. Atom Sci.* 3: 347/47). N.B. bibliography on bacterial warfare (*Bull. Atom. Sci.* 3: 364/47). P. B. Medawar writes on cellular inheritance and transformation (*Biol. Rev. Cambridge Philo. Soc.* 22: 360/47). New illustrated edition planned for *Letheon: the Cadenced Story of Anesthesia,* since 1st ed. is exhausted (Univ. Texas Press, Austin, '48, available from Univ. Texas Med. Branch Library, Galveston, at $2.50).

FEBRUARY, 1948

1. NEUROPSYCHIATRY: P. Gruenwald discloses high incidence of mental deficiency of prenatal origin (*Am. J. Med. Sci.*, 214:605, 1947). H. Cohen discusses increase and decrease of referred pain of visceral origin (*Lancet*, 2:934, Dec. 27, 1947). L. R. Wolberg describes hypnoanalysis in relation to psychoanalytic therapy (*Am. J. Psychotherapy*, 1:412, 1947). E. B. Jackson discusses learning and discipline (*Am. J. Orthopsych.*, 17:580, 1947). W. R. Hess reviews autonomic function and the mid-brain (*Helv. Physiol. Pharmacol. Acta*, Suppl. 4, Schwabe, Basle, 1948, 90 pp., 12 SwFr.). H. J. Eysenck surveys *Dimensions of Personality* (Kegan, Paul.

London, 1947, 317 pp., 25s). T. Benedek interprets *Insight and Personality Adjustment* (Ronald, N.Y. 10, 1947, 307 pp., $4). M. Sherman analyses *Intelligence and Its Deviations* (Ronald, N.Y., 1948, 300 pp., $3.75). L. J. Saul offers *Emotional Maturity: The Dynamics of Personality* (Lippincott. Phila., 1948, 338 pp., $5). A. D. Hart might bookify Psychosomatic Diagnosis (*J.A.M.A.*, 136:147, Jan. 17, 1948). G. Murphy also surveys *Personality: A Biosocial Approach to Origins and Structure* (Harper, N.Y., 1947, 999 pp., $5). H. M. Pollock discusses *Mental Disease and Social Welfare* (State Hosp. Press, Utica, N.Y., 1947, 237 pp., $2). D. B. Barron speculates on far afield symbolism may go (*Psychoanal. Rev.*, 34:395, 1947). B. Karpman notes moral agenesis (*Psycho. Quart.*, 21:361, 1947). R. Conteaux well reviews dope on myoneural synapse (*Rev. Canad. Bio.*, 6:563, 1947). J. P. Scott offers comparative data on dominance and frustration-aggression hypothesis (*Physiol. Zool.*, 21:31, 1948). R. Derom revives bismuth prophylaxis of syphilis (*Rev. Belge. Path. Med. Exp.*, 18:101, 1947).

2. PHARMACOLOGY: H. M. Evans surveys recent work on hormones of anterior pituitary (*J. de Physiol.*, 39:121, 1947). G. Valette and R. Cavier discuss cutaneous absorption (*Ibid.* p. 137). F. M. Berger finds myanesin acts by selective depression of spinal cord (*Brit. J. Pharmacol.*, 2:241, 1947). G. W. Hayward finds tetraethyl ammonium bromide temporarily helpful in hypertensive heart failure (*Lancet*, 2:18, Jan. 3, 1948). W. Seifriz revives J. Blake's century-old notion (*Am. J. Med. Sci.*, 15:63–76, 1848) on relation between isomorphism and isosterism and biological action (*Science*, 107:15, Jan. 2, 1948). M. L. Ahuja and others find heparin neutralizes venoms of viperine snakes (*Ind. J. Med. Res.*, 35:227, 1947). W. Anderson discusses physico-chemical aspects of chemical carcinogens in relation to energy transfer (*Nature*, 160:893, Dec. 27, 1947). R. R. MacIntosh and W. W. Mushin offer well illustrated *Physics for the Anesthetist* (C. C. Thomas, Springfield, Ill., 1947, 241 pp., $7.50). E. B. Verney's Croonian Lecture covers antidiuretic hormone and factors determining its release (*Proc. Roy. Soc. B.*, 135:25, Dec., 1947). R. A. Hemphill finds tannin internally helpful in intestinal allergy (*Acta. Med. Scand.*, 129:56, 1947). H. Colldahl recommends glucose in hypnotic poisoning, especially with barbitals (*Ibid.*, p. 257). M. Friedman and R. Bine show excess potassium inhibits cardiac effects of digitalis glycosides (*Am. J. Med. Sci.*, 214:633, 1947). M. M. Hartman (*Ann. Allergy*, 5:536, 1947) confirms G. Lehman and P. K. Knoefel (*J. Pharmacol.*, 80:335, 1944) on anti-spasmodic and sedative action of trasentin-like 9, 10-dihydroanthracene diethylamino ethyl carboxylate. R. T. Williams discusses *Detoxication Mechanisms* (Chapman and Hall, London, 1948, 296 pp., 25s). S. Gollan and others describe a non-toxic hypertensinase from wheat bran effective IV (*J. Exp. Med.*, 87:29, 1948). D. Marsh and C. Ross describe pressor action of cyclopentyl ethyl amines (*J. Pharmacol.*, 91:324, 1947). J. Finnegan and others study nicotine excretion (*Ibid.*, p. 357).

3. Et Alia: H. P. Himsworth *Lectures on the Liver and Its Diseases* (Blackwell, Oxford, 1947, 220 pp., 18s 6d). A. T. Cameron reviews *Taste Sense and Relative Sweetness* (Sugar Res. Fd., Sci. Rep. Ser. No. 9, N.Y., Dec., 1947). Note symposium on schistosomiasis (Nat. Inst. Health, Bull. 189, Washington, 1947, 212 pp.). N. B. symposium on pernicious anemia opening serial Festschrift for G. R. Monot (*Blood*, 3:5–127, 1948). R. J. V. Pulvertaft discusses post-operative pulmonary embolism (*Ann. Roy. Coll. Surg. Eng.*, 1:181, 1947). J. Albert and M. B. Abad show 12 yr. cyclic incidence of beri-beri in Philippines and indicate factors other than thiamin in etiology (*Acta. Med. Philip*, 4:7, 1947). R. F. A. Dean and R. A. McCance show renal clearances for urea and NaCl are much lower in infants than in adults (*Nature*, 160:904, Dec. 27, 1947). J. D. Adams and G. K. Coonse discuss bursitis (*Occup. Med.*, 4:137, 1947). A. C. M. Lips and others find no correlation between blood histamine levels and peptic ulcer (*Acta. Med. Scand.*, 129:274, 1947). J. G. Allen and others note heparinemia after exposure to large doses of ionizing radiation (*J. Exp. Med.*, 87:71, 1948). D. Davis reminds spinal nerve root pain (radiculitis) may simulate symptoms of coronary disease (*Am. Heart J.*, 35:70, 1948). A. Fagraeus says antibodies are formed in reticulo-endothelial system especially in plasma cells (*J. Immunol*, 58:1, 1948). J. W. Heard reviews purified animal viruses (*Ibid.*, p. 49). H. Goldblatt introduces symposium series on hypertension (*Am. J. Med.*, 4:100, 1948). D. B. Tresidder discusses aims of medical education (*J. Asso. Am. Med. Coll.*, 23:8, 1948).